



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(51) International Patent Classification:</b><br><b>C07D 471/04, A61K 31/519,</b><br><b>A61P 9/00, A61P 25/00,</b><br><b>C07D 221/00, C07D 239/00,</b><br><b>C07D 451/00, C07D 471/00,</b><br><b>C07D 519/00</b>   | <b>A1</b>        | <b>(11) International Publication Number:</b><br><b>WO 00/23444</b><br><b>(43) International Publication Date:</b><br><b>27 April 2000 (27.04.2000)</b> |
| <b>(21) International Application Number:</b> PCT/US99/24901<br><b>(22) International Filing Date:</b> 21 October 1999 (21.10.1999)<br><b>(30) Priority Data:</b><br>09/176,521 21 October 1998 (21.10.1998) US<br><b>(60) Parent Application or Grant</b><br>ABBOTT LABORATORIES [/]; (). BHAGWAT, Shripad, S.<br>[/]; (). LEE, Chih-Hung [/]; (). COWART, Marlon, D. [/];<br>(). McKIE, Jeffrey, A. [/]; (). GRILLOT, Anne, Laure [/];<br>(). STEWART, Andrew, O. [/]; (). ZHENG, Guo, Zhu [/];<br>(). PERNER, Richard, J. [/]; (). MILLER, Robert, A. ; ().  | <b>Published</b> |   |
| <b>(54) Title: 5,7-DISUBSTITUTED-4-AMINOPYRIDO[2,3-D]PYRIMIDINE COMPOUNDS</b><br><b>(54) Titre: COMPOSES DE 4-AMINOPYRIDO[2,3-D]PYRIMIDINE A DISUBSTITUTION 5,7</b>   |                  |   |
| <b>(57) Abstract</b><br><p>A method of inhibiting adenosine kinase by administering one of more compounds of formula (I), wherein R1<sub>z</sub>, R2<sub>z</sub>, R3<sub>z</sub> and R4<sub>z</sub> are defined, a pharmaceutical composition comprising a therapeutically effective amount of a compound thereof above in combination with a pharmaceutically acceptable carrier, and a method of treating cerebral ischemia, epilepsy, nociperception, inflammation and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound thereof, a process for preparing said compounds, and compounds having the above formula wherein R1<sub>z</sub>, R2<sub>z</sub>, R3<sub>z</sub> and R4<sub>z</sub> are separately defined.</p> <b>(57) Abrégé</b><br><p>Cette invention a trait à une technique d'inhibition de l'adénosine kinase par administration d'un ou de plusieurs composés correspondant à la formule (I), formule dans laquelle, R1<sub>z</sub>, R2<sub>z</sub>, R3<sub>z</sub> et R4<sub>z</sub> sont définis. Elle concerne également une composition pharmaceutique renfermant une quantité efficace du point de vue thérapeutique du composé susmentionné associé à un excipient acceptable du point de vue pharmaceutique. Elle porte, de surcroît, sur une méthode de traitement de l'ischémie cérébrale, de l'épilepsie, de la perception nociceptive, de l'inflammation et de la septicémie, laquelle méthode consiste à administrer au sujet mammalien une quantité efficace du point de vue thérapeutique de ce composé. Elle concerne, en outre, un procédé de préparation desdits composés et des composés correspondant à la formule (I), formule dans laquelle R1<sub>z</sub>, R2<sub>z</sub>, R3<sub>z</sub> et R4<sub>z</sub> sont définis séparément.</p> |                  |   |

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| <p>(21) International Application Number: PCT/US99/24901</p> <p>(22) International Filing Date: 21 October 1999 (21.10.99)</p> <p>(30) Priority Data:<br/>09/176,521 21 October 1998 (21.10.98) US</p> <p>(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD<br/>0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL<br/>60064-6050 (US).</p> <p>(72) Inventors: BHAGWAT, Shripad, S.; 5015 Ashley Falls Court,<br/>San Diego, CA 92130 (US). LEE, Chih-Hung; 966 Dunhill<br/>Road, Grayslake, IL 60030 (US). COWART, Marlon, D.;<br/>43 E. Dahlia Lane, Round Lake Beach, IL 60073 (US).<br/>McKIE, Jeffrey, A.; 5555 Oberlin Drive, San Diego, CA<br/>92121 (US). GRILLOT, Anne, Laure; Apartment #2, 99<br/>Hammond Street, Cambridge, MA 02138 (US). STEWART,<br/>Andrew, O.; 1289 Thornbury Lane, Libertyville, IL 60048<br/>(US). ZHENG, Guo, Zhu; 29609 N. Birch, Lake Bluff,<br/>IL 60044 (US). PERNER, Richard, J.; 704 Penny Lake,<br/>Gurnee, IL 60031 (US).</p> |  | <p>(74) Agents: MILLER, Robert, A. et al.; Abbott Laboratories,<br/>CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park,<br/>IL 60064-6050 (US).</p> <p>(81) Designated States: CA, JP, MX, European patent (AT, BF,<br/>CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,<br/>NL, PT, SE).</p> <p>Published<br/><i>With international search report.<br/>Before the expiration of the time limit for amending the<br/>claims and to be republished in the event of the receipt of<br/>amendments.</i></p> |   |
| <p>(54) Title: 5,7-DISUBSTITUTED-4-AMINOPYRIDO[2,3-D]PYRIMIDINE COMPOUNDS</p> <div style="text-align: center;"> <p>(I)</p> </div>   |  |  |   |
| <p>(57) Abstract</p> <p>A method of inhibiting adenosine kinase by administering one of more compounds of formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are defined, a pharmaceutical composition comprising a therapeutically effective amount of a compound thereof above in combination with a pharmaceutically acceptable carrier, and a method of treating cerebral ischemia, epilepsy, nociception, inflammation and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound thereof, a process for preparing said compounds, and compounds having the above formula wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are separately defined.</p>   |  |  |   |

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**Description**

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## 5.7-DISUBSTITUTED-4-AMINOPYRIDO[2,3-D]PYRIMIDINE COMPOUNDS

This application is a continuation in part of copending U.S. Patent Application Serial No. 09/176,521 filed October 21, 1998 which in turn is a continuation in part of copending U.S. Patent Application Serial No. 09/062,796 filed April 13, 1998, which in turn is a conversion of Provisional U.S. Patent Application Serial No. 60/043,251, filed April 16, 1997.

## TECHNICAL FIELD

The present invention relates to a method of inhibiting adenosine kinase by administering 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds to a mammal in need of such treatment, to pharmaceutical compositions containing such compounds, as well as to certain 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds.

## BACKGROUND OF THE INVENTION

Adenosine kinase (ATP:adenosine 5'-phosphotransferase, EC 2.7.1.20) is a ubiquitous enzyme which catalyzes the phosphorylation of adenosine to adenosine monophosphate (AMP), using adenosine triphosphate (ATP), preferentially, as the phosphate source. Magnesium is also required for the reaction, and the true cosubstrate is probably the  $MgATP^{2+}$  complex (Palella, et al., J. Biol. Chem. 1980, 255: 5264-5269). Adenosine kinase has been isolated from yeast (Leibach, et al., Hoppe-Sevler's Z. Physiol. Chem. 1971, 352: 328-344), a variety of mammalian sources (e.g. Miller, et al., J. Biol. Chem. 1979, 254: 2339-2345; Palella, et al., J. Biol. Chem. 1980, 255: 5264-5269; Yamada, et al., Comp. Biochem. Physiol. 1982, 71B: 367-372; Rottlan and Miras-Portugal, Eur. J. Biochem., 1985, 151: 365-371), and certain microorganisms (e.g. Lobelle-Rich and Reeves, Am. J. Trop. Med. Hyg. 1983, 32: 976-979; Datta, et al., J. Biol. Chem. 1987, 262: 5515-5521). It has been found to be present in virtually every human tissue assayed including kidney, liver, brain, spleen, placenta and pancreas (Andres and Fox, J. Biol. Chem. 1979, 254: 11388-11393).

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Adenosine kinase is a key enzyme in the control of intracellular adenosine concentration (Arch and Newsholme, Essays Biochem. 1978, 14: 82-123). Adenosine is a purine nucleoside that is an intermediate in the purine nucleotide degradation and salvage. Adenosine also has many important physiologic effects, many of which are mediated through the activation of specific ectocellular receptors, termed P1 receptors (Burnstock, in Cell Membrane Receptors for Drugs and Hormones, 1978, (Bolis and Straub, eds.) Raven, New York, pp. 107-118; Fredholm, et al., Pharmacol. Rev. 1994, 46: 143-156).

In the central nervous system, adenosine inhibits the release of certain neurotransmitters (Corradetti, et al., Eur. J. Pharmacol. 1984, 104: 19-26), stabilizes membrane potential (Rudolphi, et al., Cerebrovasc. Brain Metab. Rev. 1992, 4: 346-360), functions as an endogenous anticonvulsant (Dragunow, Trends Pharmacol. Sci. 1986, 7: 128-130) and may have a role as an endogenous neuroprotective agent (Rudolphi, et al., Trends Pharmacol. Sci. 1992, 13: 439-445). Adenosine may play a role in several disorders of the central nervous system such as schizophrenia, anxiety, depression and Parkinson's disease (Williams, M., in Psychopharmacology: The Fourth Generation of Progress, Bloom, Kupfer (eds.), Raven Press, New York, 1995, pp 643-655. Adenosine has also been implicated in modulating transmission in pain pathways in the spinal cord (Sawynok, et al., Br. J. Pharmacol., 1986, 88: 923-930), and in mediating the analgesic effects of morphine (Sweeney, et al., J. Pharmacol. Exp. Ther. 1987, 243: 657-665). Adenosine also, inhibits certain neutrophil functions and exhibits anti-inflammatory effects (Cronstein, J. Appl. Physiol. 1994, 76: 5-13). An AK inhibitor has been reported to decrease paw swelling in a model of adjuvant arthritis in rats (Firestein, et.al., Arthritis and Rheumatism, 1993, 36, S48).

Adenosine also exerts a variety of effects on the cardiovascular system, including vasodilation, impairment of atrioventricular conduction and endogenous cardioprotection in myocardial ischemia and reperfusion (Mullane and Williams, in Adenosine and Adenosine Receptors, 1990 (Williams, ed.) Humana Press, New Jersey, pp. 289-334). The widespread actions of adenosine also include effects on the renal, respiratory, gastrointestinal and reproductive systems, as well as on blood cells and adipocytes.

Adenosine, via its A<sub>1</sub> receptor activation on adipocytes, plays a role in diabetes by inhibiting lipolysis (Londos, et al., Proc. Natl. Acad. Sci. USA, 1980, 77, 2551).

Endogenous adenosine release appears to have a role as a natural defense mechanism in various pathophysiologic conditions, including cerebral and myocardial ischemia, seizures, pain, inflammation and sepsis. While adenosine is normally present at low levels in the extracellular space, its release is locally enhanced at the site(s) of excessive cellular activity, trauma or metabolic stress. Once in the extracellular space, adenosine activates specific extracellular receptors to elicit a variety of responses which tend to restore cellular function towards normal (Bruns, Nucleosides Nucleotides, 1991, 10: 931-943; Miller and Hsu, J. Neurotrauma, 1992, 9: S563-S577). Adenosine has a half-life measured in seconds in extracellular fluids (Moser, et al., Am. J. Physiol., 1989, 25: C799-C806), and its endogenous actions are therefore highly localized.

The inhibition of adenosine kinase can result in augmentation of the local adenosine concentrations at foci of tissue injury, further enhancing cytoprotection. This effect is likely to be most pronounced at tissue sites where trauma results in increased adenosine production, thereby minimizing systemic toxicities.

Pharmacologic compounds directed towards adenosine kinase inhibition provide potentially effective new therapies for disorders benefited by the site- and event-specific potentiation of adenosine. Disorders where such compounds may be useful include ischemic conditions such as cerebral ischemia, myocardial ischemia, angina, coronary artery bypass graft surgery (CABG), percutaneous transluminal angioplasty (PTCA), stroke, other thrombotic and embolic conditions, and neurological disorders such as epilepsy, anxiety, schizophrenia, nociperception including pain perception, neuropathic pain, visceral pain, as well as inflammation, arthritis, immunosuppression, sepsis, diabetes and gastrointestinal dysfunctions such as abnormal gastrointestinal motility.

A number of compounds have been reported to inhibit adenosine kinase. The most potent of these include 5'-amino-5'-deoxyadenosine (Miller, et al., J. Biol. Chem., 1979, 254: 2339-2345), 5-iodotubercidin (Wotring and Townsend, Cancer Res., 1979, 39: 3018-3023) and 5'-deoxy-5-iodotubercidin (Davies, et al., Biochem. Pharmacol., 1984, 33: 347-355).

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Adenosine kinase is also responsible for the activation of many pharmacologically active nucleosides (Miller, et al., J. Biol. Chem., 1979, 254: 2339-2345), including tubercidin, formycin, ribavirin, pyrazofurin and 6-(methylmercapto)purine riboside. These purine nucleoside analogs represent an important group of antimetabolites which possess cytotoxic, anticancer and antiviral properties. They serve as substrates for adenosine kinase and are phosphorylated by the enzyme to generate the active form. The loss of adenosine kinase activity has been implicated as a mechanism of cellular resistance to the pharmacological effects of these nucleoside analogs (e.g. Bennett, et al., Mol. Pharmacol., 1966, 2: 432-443; Caldwell, et al., Can. J. Biochem., 1967, 45: 735-744; Suttle, et al., Europ. J. Cancer, 1981, 17: 43-51). Decreased cellular levels of adenosine kinase have also been associated with resistance to the toxic effects of 2'-deoxyadenosine (Hershfield and Kredich, Proc. Natl. Acad. Sci. USA, 1980, 77: 4292-4296). The accumulation of deoxyadenosine triphosphate (dATP), derived from the phosphorylation of 2'-deoxyadenosine, has been suggested as a toxic mechanism in the immune defect associated with inheritable adenosine deaminase deficiency (Kredich and Hershfield, in The Metabolic Basis of Inherited Diseases, 1989 (Scriver, et al., eds.), McGraw-Hill, New York, pp. 1045-1075).

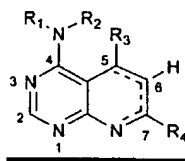
B.S. Hurlbert et al. (J. Med. Chem., 11: 711-717 (1968)) disclose various 2,4-diaminopyrido[2,3-d]pyrimidine compounds having use as antibacterial agents. R. K. Robins et al. (J. Amer. Chem. Soc., 80:3449-3457 (1958)) disclose methods for preparing a number of 2,4-dihydroxy-, 2,4-diamino-, 2-amino-4-hydroxy- and 2-mercapto-4-hydroxypyrido[2,3-d]pyrimidines having antifolate activity. R. Sharma et al., (Indian J. Chem., 31B: 719-720 (1992)) disclose 4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine and 4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine compounds having antibacterial activity. A. Gupta et al., (J. Indian Chem. Soc., 71: 635-636 (1994)) disclose 4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine and 4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine compounds having antibacterial activity. L. Prakash et al., Pharmazie, 48: 221-222 (1993)) disclose 4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine, 4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-

d]pyrimidine, 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine, and 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine compounds having antifungal activity. P. Victory et al., Tetrahedron, 51: 10253-10258 (1995)) discloses the synthesis of 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine compounds from acyclic precursors. Bridges et al. (PCT application WO 95/19774, published July 27, 1995) disclose various bicyclic heteroaromatic compounds as having utility for inhibiting tyrosine kinase of epidermal growth factors.

## SUMMARY OF THE INVENTION

The present invention provides for 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds having utility as adenosine kinase inhibitors.

In one aspect, the present invention provides a method of inhibiting adenosine kinase by administering a compound of formula I



I,

or a pharmaceutically acceptable salt or amide thereof in vitro or to a mammal wherein,

$R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclecarbonyl, hydroxyalkyl, iminoalkyl, and  $(NZ_1Z_2)$ alkyl, or  $R^1$  and  $R^2$  may join together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

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$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ,Z<sub>2</sub>)alkyl, and  $-R^A R^D$ ;

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$R^A$  is selected from the group consisting of aryl and arylalkyl;

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$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

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$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

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$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl;

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$R^E$  is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and,

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a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

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with the proviso that the following compounds are excluded,

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

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4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine, and

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4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

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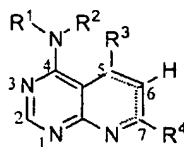
In particular, the method of inhibiting adenosine kinase comprises exposing an adenosine kinase to an effective inhibiting amount of a compound of Formula I of the present invention. Where the adenosine kinase is located in vivo, the compound is administered to the organism.

In still another aspect, the present invention provides a method of treating ischemia, neurological disorders, nociperception, inflammation, immunosuppression, gastrointestinal disfunctions, diabetes and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Formula I of the present invention.

In a preferred aspect, the present invention provides a method of treating cerebral ischemia, myocardial ischemia, angina, coronary artery bypass graft surgery, percutaneous transluminal angioplasty, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, pain perception, neuropathic pain, visceral pain, arthritis, sepsis, diabetes and abnormal gastrointestinal motility in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Formula I of the present invention.

The present invention also contemplates the use of pharmaceutically acceptable salts and amides of compounds having Formula I.

In another aspect, the present invention provides a compound of formula I



or a pharmaceutically acceptable salt or amide thereof wherein

$R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclecarbonyl, hydroxyalkyl, iminoalkyl, and  $(NZ, Z_1)$ alkyl, or  $R^1$  and  $R^2$  may join

together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxy carbonyl, alkyl, alkyl carbonyl, benzyl, benzyloxy carbonyl, and formyl;

$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl,  $(NZ_1Z_2)$ alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl;

$R^E$  is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

with the proviso that the compound may not be selected from the group consisting of:

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;



4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

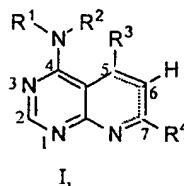
4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine; and

4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I above in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a process for the preparation of adenosine kinase inhibiting compounds of formula I



wherein

$R^1$  and  $R^2$  are hydrogen;

$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl,  $(NZ)_2$ alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl,

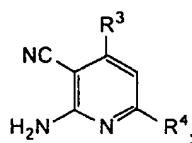
heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

$R^E$  is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

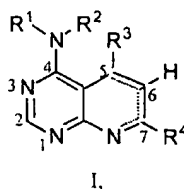
the method comprising

- (a) reacting a ketone having the formula  $R^4-CO-CH_3$ , wherein  $R^4$  is as defined above, with an aldehyde having the formula  $R^3-CHO$ , wherein  $R^3$  is as defined above and malononitrile in the presence of an ammonium salt under anhydrous conditions and isolating a first intermediate compound having the structure



- (b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5,6 carbons and a double bond between the 7 carbon and the 8 nitrogen, and then,
- (c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

- In another aspect, the present invention provides a process for the preparation of adenosine kinase inhibiting compounds of formula I



I,

wherein

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$R^1$  and  $R^2$  are hydrogen;

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$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl,  $(NZ_1Z_2)$ alkyl, and  $-R^A R^B$ ;

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$R^A$  is selected from the group consisting of aryl and arylalkyl;

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$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

$R^1$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

20

10  $R^C$  is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

25

$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

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$R^E$  is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

35

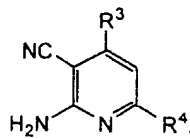
20 a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

the method comprising

40

(a) reacting a ketone having the formula  $R^4C(O)CH_3$ , wherein  $R^4$  is as defined above, with an dicyanoalkene compound having the formula  $R^3CH=C(CN)_2$ , wherein  $R^3$  is as defined above by heating at reflux and isolating a first intermediate compound having the structure

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(b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5 and 6 carbons and a double bond between the 7 carbon and the 8 nitrogen and

(c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds that are useful in inhibiting adenosine kinase, to pharmaceutical compositions containing such compounds, to a method of using such compounds for inhibiting adenosine kinase, to novel 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds and to a process of preparing 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds.

In one aspect, the present invention provides 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidine compounds that are adenosine kinase inhibitors. An adenosine kinase inhibitor of the present invention is a compound of the Formula I, shown above.

As summarized above, the present invention relates to a method of inhibiting adenosine kinase comprising administering a compound of formula I



wherein

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and (NZ,Z<sub>2</sub>)alkyl, or R<sup>1</sup> and R<sup>2</sup> may join together with the nitrogen atom to which they are attached to form a 6 membered ring

optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

$R^3$  is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocycloalkyl, (NZ, Z<sub>2</sub>)alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting of aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

$R^4$  is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl and heterocycle;

$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl;

$R^E$  is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained.

The preferred compounds utilized in the above method of inhibiting adenosine kinase are selected from a compound of formula II



II.

wherein

$R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl,

heterocyclealkyl, hydroxyalkyl, iminoalkyl, and (NZ<sub>1</sub>Z<sub>2</sub>)alkyl, or R<sup>1</sup> and R<sup>2</sup> may join together with the nitrogen atom to which they are attached to form a 6 membered ring optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

R<sup>1</sup> is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl, (NZ<sub>1</sub>Z<sub>2</sub>)alkyl, and -R<sup>A</sup>R<sup>B</sup>;

R<sup>A</sup> is selected from the group consisting of aryl and arylalkyl;

R<sup>B</sup> is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

R<sup>1</sup> is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and -R<sup>C</sup>R<sup>D</sup>R<sup>E</sup>;

R<sup>C</sup> is selected from the group consisting of aryl and heterocycle;

R<sup>D</sup> is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl; and

R<sup>E</sup> is absent or is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl.

In a preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula II above, wherein R<sup>4</sup> is aryl or heterocycle and substituted versions thereof or -R<sup>C</sup>R<sup>D</sup>R<sup>E</sup>.

In a more preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula II above, wherein R<sup>4</sup> is aryl or heterocycle and substituted versions thereof and R<sup>3</sup> is alkyl, aryl, arylalkyl or heterocycle and substituted versions thereof wherein the substituents are as identified above.

In another preferred embodiment, an adenosine kinase inhibitor of the present invention is a compound of Formula I above, wherein R<sup>4</sup> is selected from the group consisting of: phenyl; thiophene-2-yl; 3-methyl-2-oxobenzoxazolin-6-yl; 2-(dimethylamino)-5-pyrimidinyl; 2-(N-formyl-N-methyl amino)-5-pyrimidinyl; 2-(N-

5 methoxyethyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methylamino)-5-pyrimidinyl; 2-(1-morpholinyl)-5-pyrimidinyl; 2-(1-pyrrolidinyl)-5-pyrimidinyl; 2-dimethylamino-5-pyrimidinyl; 2-furanyl; 2-oxobenzoxazolin-6-yl; 2-pyridyl; 3-(dimethylamino)phenyl; 3-amino-4-methoxyphenyl; 3-bromo-4-(dimethylamino)phenyl; 3-methoxyphenyl; 3-methyl-4-(N-acetyl-N-methylamino)phenyl; 3-methyl-4-(N-formyl-N-methylamino)phenyl; 3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl; 3-methyl-4-(N-methylamino)phenyl; 3-methyl-4-pyrrolidinylphenyl; 3-pyridyl; 3,4-dichlorophenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 4-(acetylamino)phenyl; 4-(dimethylamino)-3-fluorophenyl; 4-(dimethylamino)phenyl; 4-(imidazol-1-yl)phenyl; 4-(methylthio)phenyl; 4-(morpholinyl)phenyl; 4-(N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-(2-methoxyethyl)amino)phenyl; 4-(N-acetyl-N-methylamino)phenyl; 4-(N-ethyl-N-formylamino)phenyl; 4-(N-ethylamino)phenyl; 4-(N-formyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-isopropylamino)phenyl; 4-(N-methyl-N-(2-dimethylamino)ethyl)amino)phenyl; 4-(N-methyl-N-(2-N-phthalimidyl)acetyl)amino)phenyl; 4-(N-methyl-N-(2-cyano)ethylamino)phenyl; 4-(N-methyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-methyl-N-(3-methoxy)propionylamino)phenyl; 4-(N-methyl-N-acetyl)amino)phenyl; 4-(N-methyl-N-formylamino)phenyl; 4-(N-methyl-N-trifluoroacetyl)amino)phenyl; 4-(N-morpholinyl)phenyl; 4-(thiophene-2-yl)phenyl; 4-(ureido)phenyl; 4-(2-(dimethylamino)acetyl)amino)phenyl; 4-(2-(2-methoxy)acetyl)amino)ethyl)amino)phenyl; 4-(2-methoxy)ethoxyphenyl; 4-(2-oxo-3-oxazolidinyl)phenyl; 4-(4-methoxy-2-butyl)phenyl; 4-(4-methylpiperidinyl)phenyl; 4-(5-pyrimidinyl)phenyl; 4-aminophenyl; 4-bromophenyl; 4-butoxyphenyl; 4-carboxamidophenyl; 4-chlorophenyl; 4-cyanophenyl; 4-diethylaminophenyl; 4-diethylmalonylallylphenyl; 4-dimethylaminophenyl; 4-ethoxyphenyl; 4-ethylphenyl; 4-fluorophenyl; 4-hydroxyphenyl; 4-imidazolylphenyl; 4-iodophenyl; 4-isopropylphenyl; 4-methoxyphenyl; 4-methylaminophenyl; 4-methylsulfonylphenyl; 4-morpholinylphenyl; 4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl; 4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl; 4-N-ethyl-N-(2-methoxyethyl)amino)phenyl; 4-N-formylpiperazinylphenyl; 4-nitrophenyl; 4-piperidinylphenyl; 4-(3-pyridyl)phenyl; 4-pyrrolidinylphenyl; 4-t-butylacrylphenyl; 5-

(dimethylamino)thiophene-2-yl; 5-amino-2-pyridyl; 5-dimethylamino-2-pyrazinyl; 3-dimethylaminopyridazin-6-yl; 5-dimethylamino-2-pyridyl; 5-pyrimidinylphenyl; 6-(N-methyl-N-formylamino)-3-pyridinyl; 6-(N-methyl-N-methoxyethylamino)-3-pyridinyl; 6-(2-oxo-3-oxazolidinyl)-3-pyridinyl; 6-dimethylamino-3-pyridinyl; 6-imidazolyl-3-pyridinyl; 6-morpholinyl-3-pyridinyl; 6-pyrrolidinyl-3-pyridinyl; 6-(2-propyl)-3-pyridinyl; (4-formylamino)phenyl; 6-(4-oxopiperidinyl)-3-pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl; 6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl; 6-(4-methoxyiminopiperidinyl)-3-pyridazinyl; 6-phenylmethoxy-3-pyridazinyl; 6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl; 6-(1,3-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl; 6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl; 6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide; 2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl; 5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl; 2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-(4-methoxypiperidinyl)-3-pyridyl; 6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl; 6-isopropoxy-3-pyridazinyl; 6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranyloxy)-3-pyridazinyl; 6-morpholinylethoxy-3-pyridazinyl; 6-(4-ethoxypiperidinyl)-3-pyridazinyl; 6-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl; 6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4.5-c]pyrrol-5-yl)-3-pyridyl; 6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl; 6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(3-(S)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxypyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(trans-3,4-bis-



5 ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-  
3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl;  
10 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3-amino-4-  
hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-  
5 (1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(4-tertbutyl)piperidinyl)-3-  
pyridazinyl; 6-(4-N-formyl)piperidinyl)-3-pyridazinyl; 6-morpholinyl)-3-pyridazinyl; 4-N-  
1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide; 4-(4-dioxo-8-  
15 azaspiro[4.5]decan-8-ylcarboxamide)phenyl; 6-(3-methoxy-1,5-dioxo-9-  
azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(1,5-dioxo-3-hydroxymethyl-9-  
20 azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-  
pyridazinyl; 6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2R,3R)-  
2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2S,3S)-  
2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-(4,4-(cis-1,2-  
25 dioxycyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1S,2S-  
15 dimethoxymethylethanedioxy)piperidinyl)-3-pyridazinyl; 6-(4,4-(cis-3,4-dioxy-  
oxacyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-  
methoxypropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-  
30 hydroxymethylpropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(2-(2,2-spiro-  
oxacyclopropane-1,3-dioxypropylene)piperidinyl)-3-pyridazinyl; 6-morpholinyl)-3-  
20 pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridyl; 6-(4-(N-  
methylpiperazinyl)iminopiperidinyl)-3-pyridyl; 6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-  
35 3-pyridyl; 6-(4-ethylpiperidinylcarboxylate)-3-pyridyl; 2-phenylmethyl-3(2H)-  
pyridazinone-6-yl; 6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-  
morpholinylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N,N-  
40 25 dimethylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methyl-N-  
methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-  
methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-hydroxymethylpiperidinyl)-3-  
45 pyridyl; 6-(4-hydroxypiperidinyl)-3-pyridyl; 6-(4-N-acetyl)piperazinyl)-3-pyridyl; 6-(4-  
cyanopiperidinyl)-3-pyridyl; 6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl; 4-  
30 morpholinylbenzenesulfonamide; 4-N-4,4-ethylenedioxy piperidinylbenzenesulfonamide;

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4-N-cyclopropylbenzenesulfonamide; 4-piperidinebenzenesulfonamide; 4-(4-cyanopiperidine)benzenesulfonamide; 4-N-cyclopropylmethylbenzenesulfonamide; 4-N,N-dimethylaminobenzenesulfonamide; 4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide; 4-(4-hydroxypiperidine)benzenesulfonamide; 4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide; 3-fluoro-4-thiomorpholinylphenyl; 6-(thiomorpholinyl)-3-pyridyl; 6-(4,4-dioxothiomorpholinyl)-3-pyridyl; 4-(4,4-ethylenedioxy-piperidinylcarboxamide)phenyl; 4-(N-cyclopropylcarboxamide)phenyl; 4-(morpholinylcarboxamide)phenyl; 6-N-cyclopropylamino-3-pyridyl; 4-(4-hydroxypiperidinylcarboxamide)phenyl; 6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl; 6-hexahydropyrimidine-3-pyridyl; 6-(S)-2-ethoxyethoxypyrrolidinyl-3-pyridyl; 6-(R)-2-ethoxyethoxypyrrolidinyl-3-pyridyl; 6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-[(3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-2-one-5-yl]-3-pyridyl; 6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl; 6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane-3-pyridyl; 6-(2-imidizolidone-1-yl)-3-pyridyl; 4-(2,4-(1H,3H)-quinazolin-3-yl)phenyl; 6-morpholinylcarboxamide-3-pyridazinyl; 6-methoxy-3-pyridazinyl; 6-N,N-diethoxyethylamino-3-pyridazinyl; 6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranylmethyl)piperidinyl)-3-pyridazinyl; 6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl; 6-N-methyl-N-1,3-dioxalanemethylamino-3-pyridazinyl; 6-(4,4-dioxyethylenecyclohexyloxy)-3-pyridazinyl; 6-dihydroxymethylmethoxy-3-pyridazinyl; 6-(3-pyridyloxy)-3-pyridazinyl; 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl; 6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl; 6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(3-hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl; 6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl; 6-(2-(4-

5 tetrahydropyranyloxy)iminopiperidiny)-3-pyridazinyl; 2-morpholinyl-5-thiazoyl; 5-  
bromo-2-thienyl; 2,5-dimethyl-3-thienyl; 5-chloro-2-thienyl; 2,4-dimethyl-5-thiazoyl; 5-  
10 methyl-2-thienyl; 2-furanyl; 2-(4,4-dioxyethylenepiperidiny)-5-thiazoyl; 3-thienyl; 3-  
methyl-2-thienyl; 2-morpholinyl-4-thiazoyl; 2-morpholinyl-4-trifluoromethyl-5-thiazoyl;  
5 5-morpholinyl-2-thienyl; 4-methyl-2-morpholinyl-5-thiazoyl; 2,5-dichloro-3-thienyl; 2,5-  
dimethyl-3-furanyl; N-methyl-2-pyrrolyl; 2-N,N-dimethylamino-5-thiazoyl; 2-  
15 morpholinyl-5-thiazoyl; 2-(4,4-dioxythiomorpholinyl)-5-thiazoyl; 1-N-methyl-2-  
morpholinyl-5-imidazolyl; 2-morpholinyl-5-oxazolyl; 2-N-methyl-N-methoxyethylamino-  
5-thiazoyl; 2-N-methyl-N-ethylamino-5-thiazoyl; 2-N-pyrrolidinyl-5-thiazoyl; 2-N-  
10 methyl-N-propylamino-5-thiazoyl; 2-N,N-diethylamino-5-thiazoyl; 2-(N-  
methypiperazinyl)-5-thiazoyl; 2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl; 2-N-methyl-N-(2-  
20 pyridylethyl)-5-thiazoyl; 2-(4-oxopiperazinyl)-5-thiazoyl; 2-(4-(N-  
morpholinyl)iminopiperazinyl)-5-thiazoyl; 6-N-morpholine-3-pyridinesulfonamide; 2-(4-  
25 oxopiperidiny)-5-pyrimidyl; 2-(4,4-dioxethylenepiperidiny)-5-pyrimidyl; 5-(4,4-  
dioxethylenepiperidiny)-2-pyrazinyl; 5-(4-oxopiperidiny)-2-pyrazinyl; 6-N-cyclopropyl-  
3-pyridinesulfonamide; 6-N-(4,4-dioxethylenepiperidiny)-3-pyridinesulfonamide; 2-(4-  
30 (4-tetrahydropyranyloxy)iminopiperidiny)-5-pyrazinyl; 6-(4-  
(phenylmethoxy)iminopiperidiny)-3-pyridyl; 6-(4-(tert-butyloxy)iminopiperidiny)-3-  
pyridyl; 6-(4-(cyclohexyloxy)iminopiperidiny)-3-pyridyl; 6-(4-hydroxyiminopiperidiny)-  
20 3-pyridyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidiny)-3-pyridyl; 6-(4-  
35 methoxyethoxyiminopiperidiny)-3-pyridyl; 6-(4-(2-thenylmethoxy)iminopiperidiny)-3-  
pyridyl; 6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidiny)-3-pyridyl; 6-(4-(1-(4-  
tetrahydropyranyloxy)iminoethyl)-4-hydroxypiperidiny)-3-pyridazinyl; 6-(4-(4'-acetyl-  
4'-hydroxypiperidiny)-3-pyridazinyl; 6-(4-(1-(isopropylcarbonylmethoxy)iminoethyl)-4-  
40 4-hydroxypiperidiny)-3-pyridyl; 6-(4-(1-(ethylcarbonylmethoxy)iminoethyl)-4-  
25 hydroxypiperidiny)-3-pyridyl; 6-(4-(1-(methylcarbonylmethoxy)iminoethyl)-4-  
hydroxypiperidiny)-3-pyridyl; 6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl)-4-  
45 hydroxypiperidiny)-3-pyridyl; 6-(4-(1-(allyloxy)iminoethyl)-4-hydroxypiperidiny)-3-  
pyridyl; 6-(4-(1-(ethoxy)iminoethyl)-4-hydroxypiperidiny)-3-pyridyl; 6-(4-(1-  
30 (methoxy)iminoethyl)-4-hydroxypiperidiny)-3-pyridyl; 6-(4-(1-(hydroxy)iminoethyl)-4-

hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl;  
 6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(1-(4-  
 tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(3-  
 butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-butyrolactone)-4-  
 hydroxypiperidinyl)-3-pyridazinyl; 6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl; 6-(3-  
 hydroxyazetidyl)-3-pyridyl; 6-(cis-3-hydroxytropanyl)-3-pyridyl; 6-(cis-2,3-  
 dihydroxypiperidinyl)-3-pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl;  
 6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl; 6-(4-(N-4'-methoxyphenylcarbonyl)piperidinyl)-  
 3-pyridazinyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(trans-3,4-bis(N-  
 4'-methoxyphenylcarbonyl)pyrrolidinyl)-3-pyridyl; 6-(trans-3-hydroxytropanyl)-3-  
 pyridyl; 6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-(R,R-trans-3,4-  
 dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl;  
 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-  
 triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolyl)piperidinyl)-  
 3-pyridazinyl; 6-(4-oxothiomorpholinyl)-3-pyridyl; 6-(4-(2-keto-1-  
 benzimidazolyl)piperidinyl)-3-pyridyl; 6-(N-methyl-N-(2-pyridylethyl)amino)-3-  
 pyridyl; 6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl; 6-N-(3-pyridylmethyl)amino-3-  
 pyridyl; 6-(2-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(4-  
 bromophenyl)piperidinyl)-3-pyridyl; 6-(4-N-(2-pyridyl)piperazinyl)-3-pyridyl; 6-(4-N-  
 (2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl; 6-(4,4-diacetoxyethylthio)piperidinyl)-3-  
 pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridyl; 6-(4-pyrrolidinylpiperidinyl)-  
 3-pyridyl; 6-(4-N-cyanomethylpiperazinyl)-3-pyridyl; 6-(3-hydroxypyrrolidinyl)-3-pyridyl;  
 6-(4-methylpiperidinyl)-3-pyridyl; 6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl; 6-(4,4-  
 difluoropiperidinyl)-3-pyridyl; 6-(4,4-dioxythiomorpholinyl)-3-pyridazinyl; 6-  
 thiazolidinyl)-3-pyridyl; 6-(1,1-dioxythiazolidinyl)-3-pyridyl; 6-thiomorpholinyl)-3-  
 pyridazinyl; 6-(2,5-dihydropyrrolyl)-3-pyridyl; 6-hydroxy-3-pyridazinyl; 6-piperidinyl)-3-  
 pyridyl; and 6-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridyl; 6-morpholinyl)-3-  
 pyridyl.

In another preferred embodiment, an adenosine kinase inhibitor of the present  
 invention is a compound of Formula I above, wherein R<sup>1</sup> is selected from the group

consisting of: (thiophene-2-yl)methyl; (thiophene-3-yl)methyl; butyl; cycloheptyl; pentyl; thiophene-2-yl; 1-(3-bromophenyl)ethyl; 2-(N-phenylmethoxycarbonyl)aminophenyl; 2-(3-bromophenyl)ethyl; 2-(3-cyanophenyl)methyl; 2-(4-bromophenyl)ethyl; 2-(5-chloro-2-(thiophen-3-yl)phenyl); 2-bromophenyl; 2-furanyl; 2-methylpropyl; 2-phenylethyl; phenylmethyl; 2,3-dimethoxyphenyl; 2,3-methylenedioxyphenyl; 3-(furan-2-yl)phenyl; 3-(thiophen-2-yl)phenyl; 3-(2-pyridyl)phenyl; 3-(3-methoxybenzyl)phenyl; 2-(3-aminopropynyl)phenylmethyl; 3-benzyloxyphenyl; 3-bromo-4-fluorophenyl; 3-bromo-5-iodophenyl; 3-bromo-5-methoxyphenyl; 3-bromophenyl; 3-bromophenylmethyl; 3-carboxamidophenyl; 3-chlorophenyl; 3-cyanophenyl; 3-diethylmalonylallylphenyl; 3-dimethylaminophenyl; 3-ethoxyphenyl; 3-fluoro-5-trifluoromethylphenyl; 3-fluorophenyl; 3-hydroxyphenyl; 3-iodophenyl; 3-methoxyethoxyphenyl; 3-methoxyphenyl; 3-methylphenyl; 3-methylsulfonylphenyl; 3-methylthiophenyl; 3-t-butylacrylphenyl; 3-trifluoromethoxyphenyl; 3-trifluoromethylphenyl; 3-vinylpyridinylphenyl; 3,4-dichlorophenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 3,5-di(trifluoromethyl)phenyl; 3,5-dibromophenyl; 3,5-dichlorophenyl; 3,5-dimethoxyphenyl; 3,5-dimethylphenyl; 4-(2-propyl)phenyl; 4-(2-propyl)oxyphenyl; 4-benzyloxyphenyl; 4-bromophenyl; 4-bromothiophene-2-yl; 4-butoxyphenyl; 4-dimethylaminophenyl; 4-fluoro-3-trifluoromethylphenyl; 4-methoxyphenyl; 4-neopentylphenyl; 4-phenoxyphenyl; 5-bromothiophene-2-yl; 5-cyclohexyl; 5-cyclopropyl; 5-hexyl; 5-methyl; 5-phenyl; (2-bromo-5-chlorophenyl)methyl; (2-bromophenyl)methyl; (5-chloro-2-(3-methoxyphenyl)phenyl)methyl; 3-bromophenyl; 2-pyridyl; 2-ethoxyphenyl; 5-ethoxyphenyl; 2,5-dichlorophenyl; 2,5-dimethylphenyl; 3-fluorophenyl; 3-trifluoromethylphenyl; 5-trifluoromethylphenyl; 3,5-dichlorophenyl; 4-bromo-2-thienyl; 3-bromo-2-thienyl; 3-cyanophenyl; 4-tetrahydropyranyl; 3-indolyl; 5-indolyl; 4-quinolyl; 2-bromophenyl; 4-fluorophenyl; 4,4-difluorocyclohexyl; 1,1-dimethyl-3-butenyl; 2,3-dichlorophenyl; isopropyl; and 2-trifluorophenylphenyl.

Exemplary and preferred adenosine kinase inhibitor compounds of the invention utilized in the method recited herein include the compounds listed below wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are as described in Formula I in the specific compound:

4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(4-(2-propyl)phenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-butyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine.

20

4-amino-5-(4-(2-propyl)oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(4-benzoyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(4-(2-propyl)phenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-

d]pyrimidine.

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4-amino-5-(4-(2-propyl)phenyl)-7-(4-t-butylacetylphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

20

4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

35

d]pyrimidine.

4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine.

4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

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25

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine.

4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

45

d]pyrimidine.

4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

30

d]pyrimidine.

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4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-benzyloxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

15

d]pyrimidine,

4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

20

d]pyrimidine,

4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-phenylpyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine,

4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine.

45

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(4-(imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

10 d]pyrimidine.

20

4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3,4-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

25

d]pyrimidine.

15

4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine.

30

4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

20

4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

35

4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine.

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25

4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine.

45

4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyethoxyphenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-

15

d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-bromothiophene-2-yl)-7-(4-dimethylaminophenyl)pyrido[2,3-

30

d]pyrimidine,

4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-

20

d]pyrimidine,

4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

35

d]pyrimidine,

4-amino-5-(5-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-

d]pyrimidine,

40

25

4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-d]pyrimidine,

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4-(4-fluorophenyl)amino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine.

5

4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-

15

d]pyrimidine,

4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

d]pyrimidine,

10

4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

20

d]pyrimidine,

4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-

d]pyrimidine,

25

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

15

d]pyrimidine,

4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-

30

d]pyrimidine,

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

20

d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine,

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25

4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-

d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-

30

d]pyrimidine,

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5

4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetyl amino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formyl amino)phenyl)pyrido[2,3-d]pyrimidine,

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4,4-bis(acetyl amino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetyl amino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methyl amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl amino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl) amino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(N-isopropyl amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl) amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropyl amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethyl amino)ethyl)-N-formyl amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethyl amino)ethyl) amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-

d]pyrimidine,

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4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine.

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- 5 4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,
- 10 4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 5 4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 15 4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-(2-(N-phenylmethoxycarbonyl)aminoethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(cycloheptyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 15 4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 20 4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 35 4-amino-5-cyclopropyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-cyclohexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 40 4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 25 4-amino-5-methyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 45 4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,
- 30 4-amino-5-(2-(3-fluoro-5-trifluoromethylphenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

5 d]pyrimidine,

4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-

15

dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-

d]pyrimidine,

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-

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d]pyrimidine,

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)pyrido[2,3-

d]pyrimidine,

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine,

4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine,

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine,

4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine,

4-acetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine,

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4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

d]pyrimidine,

4-(methoxyacetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-

d]pyrimidine,

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4-trifluoroacetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine,

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4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-allylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

4-diacetylamino-5-(p-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyrazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine.

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4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-((thiophene-2-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-((thiophene-3-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(2-methoxy)acetyl(amino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)acetyl(amino)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinyl)phenyl)pyrido[2,3-d]pyrimidine,

60

4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

65

4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-

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diethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(1-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(1-phenylmethyl-3-piperidiny)-7-(4-

15

diethylaminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-

pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-

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d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-urcdo)phenyl)-pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-

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pyrido[2,3-d]pyrimidine,

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4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)-phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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10 4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-pyrazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)-phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine,

4-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

4-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride;

4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(3-(methoxypropynyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,

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4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-1-(N-methylamino)ethyl)phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-(1-(dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indoliny)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-diethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-(N-methyl-N-formyl)amino)phenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-

20

d]pyrimidine,

4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-

pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-cyclohexyl-7-(6-(4-acetylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-

45

pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-

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pyridyl)pyrido[2,3-d]pyrimidine.

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5 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine.

10 4-amino-5-cyclohexyl-7-(6-2-(N-(N',N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5 4-amino-5-cyclohexyl-7-(6-azetidiny-3-pyridyl)pyrido[2,3-d]pyrimidine.

15 4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

10 4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-cyclohexyl-7-(6-(2-methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine,

15 4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine,

30 4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine,

35 4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine,

40 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine,

45 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine,



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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidin;

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-

20

d]pyrimidine.

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4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-

d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(N-oxido-morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-

45

pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-

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pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl)-N-oxide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy)morpholinyl)-3-pyridylpyrido[2,3-d]pyrimidine.

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1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt;

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4-amino-5-(3-bromophenyl)-7-(4-methylenylpiperidinyl)-3-pyridylpyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridylpyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-cyclohexyl-7-(6-(4-methylenylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-

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d]pyrimidine,

4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine.

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(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyiminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-

20

pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-

20

pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranlyoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranlyoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-

30

pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2,3-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-

20

pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

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4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-

15

pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-

20

pyridazinyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

45

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxo-11-azadispiro[4.2.5.2]pentadecan-11-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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10 4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulfonamide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine.

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20 4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzenesulfonamide)pyrido[2,3-d]pyrimidine.

40

4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-

25 hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

15

4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(4-(4-dioxo-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-hexahydropyrimidine-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1.3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

25

4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

35

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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25

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxalanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

15

4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

40

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxythiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,

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5 4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-  
d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazolyl)pyrido[2,3-d]pyrimidine,  
10 4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazoyl)pyrido[2,3-  
5 d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-  
15 d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-  
10 d]pyrimidine,  
20 4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-  
d]pyrimidine,  
25 4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-  
15 d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-(2-pyridylethyl)-5-thiazoyl)pyrido[2,3-  
d]pyrimidine,  
30 4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-  
20 thiazoyl)pyrido[2,3-d]pyrimidine,  
35 4-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-  
d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-  
d]pyrimidine,  
40 4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-  
d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-  
45 pyrazinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine.

5 4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

10 4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

15 4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

20 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

25 4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcaboxymethoxy)iminoethyl)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcaboxymethoxy)iminoethyl)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcaboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

15 4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyll)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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25 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyll)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine.

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis(N-4'-

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methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

30

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

35

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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25

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)l)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)l)piperidinyl)-3-pyridylpyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine,

5

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine,

15

4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine,

10

4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

20

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

25

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridinyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethyloxyethyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethylthio)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine,

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5 4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine,  
10 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine,  
5 4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropiperidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine,  
15 4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-  
pyridazinyl)pyrido[2,3-d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,  
20 4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine,  
25 4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydropyrrolyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine,  
15 4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxo-8-azaspiro[4.5]decan-8-yl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine,  
30 4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine,  
amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-  
20 pyridyl)pyrido[2,3-d]pyrimidine,  
35 4-amino-5-isopropyl-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine,  
4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine,  
40 4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxyimino)pyrrolidinyl)-3-  
25 pyridyl)pyrido[2,3-d]pyrimidine, and  
4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-  
d]pyrimidine and pharmaceutically acceptable salts and amides thereof. In addition, the  
45 partially hydrogenated or fully hydrogenated versions wherein the 5,6 and/or the 7,8  
double bonds are hydrogenated of the compounds identified above are also included  
30 within the scope of the invention. The preferred substitution pattern on the R<sup>3</sup> group when

5 it is selected from, for example, a substituted aryl group, is having at least one substituent  
at the meta position. The preferred substitution pattern on the R<sup>4</sup> position when it is  
selected from, for example, a substituted heterocycle or aryl group, is having at least one  
10 substituent at the para position. The present invention is therefore directed to compounds  
5 of formula I or II with the variables recited as above wherein, in the case of R<sup>3</sup> selected  
from substituted aryl or heterocycle groups and R<sup>4</sup> selected from substituted aryl or  
15 heterocycle groups, the substituents on the R<sup>3</sup> group are meta and the substituents on the R<sup>4</sup>  
group are para. In addition, the present invention encompasses pro-drugs of the above  
compounds which may be active in their own right or are metabolized or converted to the  
20 non pro-drug form as exemplified above. The invention is not limited to synthetic  
versions of the claimed compounds and includes the compounds-per-se or pro-drugs or  
metabolites thereof regardless of how or where they are manufactured or made.

#### Definitions of Terms

25 15 The term "alkenyl," as used herein, refers to a straight or branched chain  
hydrocarbon containing from 2 to 6 carbons and containing at least one carbon-carbon  
double bond formed by the removal of two hydrogens. Representative examples of  
alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-  
30 butenyl, 4-pentenyl, 5-hexenyl, and the like.

20 The term "alkenyloxy," as used herein, refers to an alkenyl group, as defined  
herein, appended to the parent molecular moiety through an oxy moiety, as defined herein.  
35 Representative examples of alkenyloxy include, but are not limited to, 2-propenyloxy, 2-  
methyl-2-propenyloxy, 3-butenyloxy, 4-pentenyl, and the like.

40 25 The term "alkenyloxyimino," as used herein, refers to an alkenyloxy group, as  
defined herein, appended to the parent molecular moiety through an imino moiety, as  
defined herein. Representative examples of alkenyloxyimino include, but are not limited  
to, 2-propenyloxyimino, 2-methyl-2-propenyloxyimino, 3-butenyloxyimino, 4-  
45 pentenyloxyimino, and the like.

30 The term "alkenyloxyiminoalkyl," as used herein, refers to an alkenyloxyimino  
group, as defined herein, appended to the parent molecular moiety through an alkyl group,

5 as defined herein. Representative examples of alkenyloxyiminoalkyl include, but are not limited to, propen-2-yloxyiminomethyl, 2-[2-methylpropen-2-yloxyimino]ethyl, 2-[buten-3-yloxyimino]ethyl, 3-[penten-4-yloxyimino]propyl, and the like.

10 The term "alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

15 The term "alkoxyalkoxy," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through another alkoxy group, as defined herein. Representative examples of alkoxyalkoxy include, but are not limited to, tert-butoxymethoxy, 2-ethoxyethoxy, 2-methoxyethoxy, methoxymethoxy, and the like.

20 The term "alkoxyalkoxyalkyl," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkoxyalkyl include, but are not limited to, 2-(tert-butoxymethoxy)ethyl, 4-(2-ethoxyethoxy)butyl, 4-(2-methoxyethoxy)butyl, 2-(methoxymethoxy)ethyl, and the like.

25 The term "alkoxyalkoxyimino," as used herein, refers to an alkoxyalkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of alkoxyalkoxyimino include, but are not limited to, tert-butoxymethoxyimino, 2-(ethoxy)ethoxyimino, (2-methoxy)ethoxyimino, methoxymethoxyimino, and the like.

30 The term "alkoxyalkyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, methoxymethyl, and the like.

35 The term "alkoxyalkynyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkynyl group, as defined herein. Representative examples of alkoxyalkynyl include, but are not limited to, 3-(methoxy)propyn-1-yl, 4-(ethoxy)butyn-1-yl, and the like.

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The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxyalkylcarbonyl include, but are not limited to, 2-(ethoxy)ethylcarbonyl, 2-(methoxy)ethylcarbonyl, and the like.

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5 The term "alkoxycarbonyl," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, tert-butoxycarbonyl, ethoxycarbonyl, methoxycarbonyl, and the like.

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The term "alkoxycarbonylalkenyl," as used herein, refers to one or two alkoxycarbonyl groups, as defined herein, appended to the parent molecular moiety through an alkenyl group, as defined herein. Representative examples of alkoxycarbonylalkenyl include, but are not limited to, 3-(methoxycarbonyl)propen-1-yl, 4-(ethoxycarbonyl)buten-2-yl, 4-bis(ethoxycarbonyl)buten-2-yl, and the like.

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15 The term "alkoxycarbonylalkoxy" as used herein refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group. Representative examples of alkoxycarbonylalkoxy include methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 2-(methoxycarbonyl)ethoxy, and the like.

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20 The term "alkoxycarbonylalkoxyimino," as used herein refers to an alkoxycarbonylalkoxy group, as defined herein, appended to the parent molecular moiety through an imino group. Representative examples of alkoxycarbonylalkoxyimino include ethoxycarbonylmethoxyimino, 2-(methoxycarbonyl)ethoxyimino, and the like.

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25 The term "alkoxycarbonylalkoxyiminoalkyl," as used herein refers to an alkoxycarbonylalkoxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group. Representative examples of alkoxycarbonylalkoxyiminoalkyl include 2-(ethoxycarbonylmethoxyimino)ethyl, 2-[2-(methoxycarbonyl)ethoxyimino]ethyl, and the like.

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The term "alkoxycarbonylalkyl," as used herein, refers to an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as

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5 defined herein. Representative examples of alkoxycarbonylalkyl include, but are not limited to, 3-(methoxycarbonyl)propyl, 4-(ethoxycarbonyl)butyl, and the like.

10 The term "alkoxyimino," as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined  
15 herein. Representative examples of alkoxyimino include, but are not limited to, ethoxyimino, methoxyimino, propoxyimino, isopropoxyimino, and the like.

15 The term "alkoxyiminoalkyl," as used herein, refers to an alkoxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyiminoalkyl include, but are not limited  
20 to, 2-(ethoxyimino)ethyl, 2-(methoxyimino)ethyl, 2-(propoxyimino)ethyl, 2-(isopropoxyimino)ethyl, and the like.

20 The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl,  
25 n-pentyl, isopentyl, neopentyl, n-hexyl, and the like.

15 The term "alkylene," denotes a divalent group derived from a straight or branched chain hydrocarbon of from 1 to 3 carbon atoms. Representative examples of alkylene include, -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-.

30 The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined  
20 herein. Representative examples of alkylcarbonyl include, but are not limited, methylcarbonyl (acetyl), ethylcarbonyl, and the like.

35 The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxy group, as defined  
40 herein. Representative examples of alkylcarbonyloxy include, but are not limited, methylcarbonyloxy, ethylcarbonyloxy, and the like.

25 The term "alkylcarbonyloxyalkoxy," as used herein, refers to an alkylcarbonyloxy group, as defined herein, appended to the parent molecular moiety through an alkoxy  
45 group, as defined herein. Representative examples of alkylcarbonyloxyalkoxy include, but are not limited, 2-(methylcarbonyloxy)ethoxy, 3-(ethylcarbonyloxy)propoxy, and the like.  
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The term "alkylcarbonyloxyalkyl," as used herein, refers to an alkylcarbonyloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylcarbonyloxyalkyl include, but are not limited, 2-(methylcarbonyloxy)ethyl, 3-(ethylcarbonyloxy)propyl, and the like.

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The term "alkylcarbonyloxyalkylthio," as used herein, refers to an alkylcarbonyloxyalkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylcarbonyloxyalkylthio include, but are not limited, 2-(methylcarbonyloxy)ethylsulfanyl, 3-(ethylcarbonyloxy)propylsulfanyl, and the like.

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The term "alkylsulfonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited, methylsulfonyl, ethylsulfonyl, and the like.

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The term "alkylthio," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylsulfanyl, ethylsulfanyl, tert-butylsulfanyl, hexylsulfanyl, and the like.

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The term "alkylthioalkyl," as used herein, refers to an alkylthio group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylthioalkyl include, but are not limited, methylsulfanylmethyl, 2-(ethylsulfanyl)ethyl, and the like.

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The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 6 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, 1-butynyl and the like.

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The term "amino," refers to an  $-NZ_1Z_2$  group wherein  $Z_1$  and  $Z_2$  are appended to the parent molecular moiety through a nitrogen atom.  $Z_1$  and  $Z_2$  are independently selected from hydrogen, alkyl, alkylcarbonyl, benzyl, cycloalkyl, cycloalkylalkyl, formyl, and phenyl. Representative examples of  $-NZ_1Z_2$  include, but are not limited to, amino,

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benzylamino, methylamino, acetylamino, acetylmethylamino, cyclopropylamino, cyclopropylmethylamino, dimethylamino, phenylamino, and the like.

The term "aminoalkyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through an alkyl moiety, as defined herein.

Representative examples of aminoalkyl include, but are not limited, 3-aminopropyl, 4-dimethylaminobutyl, and the like.

The term "aminoalkylcarbonyl," as used herein, refers to an aminoalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl moiety, as defined herein. Representative examples of aminoalkylcarbonyl include, but are not limited, 3-(amino)propylcarbonyl, 4-(dimethylamino)butylcarbonyl, and the like.

The term "aminoalkynyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through an alkynyl moiety, as defined herein. Representative examples of aminoalkynyl include, but are not limited, 3-(amino)propyn-1-yl, 4-(dimethylamino)butyn-1-yl, and the like.

The term "amino-protecting group" or "N-protecting group," refers to groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used nitrogen-protecting groups are disclosed in Greene, T. W., & Wuts, P. G. M. (1991). Protective Groups In Organic Synthesis (2nd ed.). New York: John Wiley & Sons. Preferred nitrogen-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "aminosulfonyl," as used herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a sulfonyl moiety, as defined herein. Representative examples of aminosulfonyl include, but are not limited, aminosulfonyl, dimethylaminosulfonyl, diethylaminosulfonyl, and the like.

The term "aryl," as used herein, refers to a monocyclic-ring system, or a bicyclic-fused ring system wherein one or both of the fused rings are aromatic. Representative examples of aryl include, but are not limited to, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like.



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The aryl groups of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkenyloxy, alkenyloxyimino, alkenyloxyiminoalkyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyimino, alkoxyalkyl, alkoxyalkynyl, alkoxycarbonyl, alkoxycarbonylalkenyl, alkoxycarbonylalkyl, alkoxycarbonylalkoxyimino, alkoxycarbonylalkoxyiminoalkyl, alkoxyimino, alkoxyiminoalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkoxy, alkylcarbonyloxyalkyl, alkylcarbonyloxyalkylthio, alkylsulfonyl, alkylthio, alkylthioalkyl, aminoalkynyl, aminosulfonyl, azido, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkoxy, cycloalkylalkyl, cycloalkyloxy, cycloalkyloxyimino, ethylenedioxy, formyl, formylalkyl, haloalkyl, haloalkylcarbonyl, halogen, hydroxy, hydroxyalkoxy, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyimino, hydroxyiminoalkyl, methylenedioxy, methylenyl, nitro, oxo, 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one, phosphonato, spirocycle, (spirocycle)spirocycle, thioureylene, ureylene,  $-NZ_{12}Z_{13}$ ,  $(NZ_{12}Z_{13})$ alkyl,  $(NZ_{12}Z_{13})$ carbonyl, and  $(NZ_{12}Z_{13})$ carbonyloxy wherein  $Z_{12}$  and  $Z_{13}$  are independently selected from hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, aminoalkylcarbonyl, aminosulfonyl, aryl, arylalkyl, arylalkylcarbonyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, heterocyclesulfonyl, and  $(NZ_{14}Z_{15})$ alkyl wherein  $Z_{14}$  and  $Z_{15}$  are independently selected from the group consisting of hydrogen, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkyl, alkylcarbonyl, formyl, heterocycle, and hydroxyalkoxyalkyl.

The term "arylalkoxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of arylalkoxy include, but are not limited to, 2-phenylethoxy, 3-naphth-2-ylpropoxy, 5-phenylpentyl, and the like.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylalkoxycarbonyl include, but are not limited to, benzyloxycarbonyl, naphth-2-ylmethoxycarbonyl, and the like.

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The term "arylalkoxyimino," as used herein, refers to an arylalkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of arylalkoxyimino include, but are not limited to, 2-phenylethoxyimino, 3-naphth-2-ylpropoxyimino, 5-phenylpentyloxyimino, and the like.

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The term "arylalkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

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The term "(aryl)alkyl," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through another aryl group, as defined herein. Representative examples of (aryl)aryl include, but are not limited to, biphenyl, 4'-methoxybiphenyl, and the like.

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The term "aryloxy," refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthyloxy, 4-chlorophenoxy, 4-methylphenoxy, 3,5-dimethoxyphenoxy, and the like.

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The term "azido," as used herein, refers to a  $-N_3$  group.

The term "carbonyl," as used herein, refers to a  $-C(O)-$  group.

The term "carboxy," as used herein, refers to a  $-CO_2H$  group.

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The term "carboxyalkyl," as used herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

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The term "cyano," as used herein, refers to a  $-CN$  group.

The term "cyanoalkyl," as used herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cyanoalkyl include, but are not limited to, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, and the like.

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The term "cycloalkyl," as used herein, refers to a saturated cyclic hydrocarbon group containing from 3 to 8 carbons. Representative examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The cycloalkyl groups of this invention can be substituted with 1 or 2 substituents independently selected from alkenyl, alkenyloxy, alkenyloxyimino, alkenyloxyiminoalkyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyimino, alkoxyalkyl, alkoxyalkynyl, alkoxycarbonyl, alkoxycarbonylalkenyl, alkoxycarbonylalkyl, alkoxycarbonylalkoxyimino, alkoxycarbonylalkoxyiminoalkyl, alkoxyimino, alkoxyiminoalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkoxy, alkylcarbonyloxyalkyl, alkylcarbonyloxyalkylthio, alkylsulfonyl, alkylthio, alkylthioalkyl, aminoalkynyl, aminosulfonyl, azido, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkoxy, cycloalkylalkyl, cycloalkyloxy, cycloalkyloxyimino, ethylenedioxy, formyl, formylalkyl, haloalkyl, haloalkylcarbonyl, halogen, hydroxy, hydroxyalkoxy, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyimino, hydroxyiminoalkyl, methylenedioxy, methylenyl, nitro, oxo, 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one, phosphonato, spirocycle, (spirocycle)spirocycle, thioureylene, ureylene,  $-NZ_{12}Z_{13}$ ,  $(NZ_{12}Z_{13})$ alkyl,  $(NZ_{12}Z_{13})$ carbonyl, and  $(NZ_{12}Z_{13})$ carbonyloxy wherein  $Z_{12}$  and  $Z_{13}$  are independently selected from hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, aminoalkylcarbonyl, aminosulfonyl, aryl, arylalkyl, arylalkylcarbonyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, heterocyclesulfonyl, and  $(NZ_{14}Z_{15})$ alkyl wherein  $Z_{14}$  and  $Z_{15}$  are independently selected from the group consisting of hydrogen, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkyl, alkylcarbonyl, formyl, heterocycle, and hydroxyalkoxyalkyl.

The term "cycloalkylalkoxy," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of cycloalkylalkoxy include, but are not limited to, cyclopropylmethoxy, 2-cyclobutylethoxy, cyclopentylmethoxy, cyclohexylmethoxy, 4-cycloheptylbutoxy, and the like.

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The term "cycloalkylalkyl," as used herein, refers to cycloalkyl group, as defined herein; appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl and 4-cycloheptylbutyl, and the like.

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The term "cycloalkylcarbonyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of cycloalkylcarbonyl include, but are not limited to, cyclopropylcarbonyl, 2-cyclobutylcarbonyl, cyclohexylcarbonyl, and the like.

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The term "cycloalkyloxy," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of cycloalkyloxy include, but are not limited to, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

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The term "cycloalkyloxyimino," as used herein, refers to cycloalkyloxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of cycloalkyloxyimino include, but are not limited to, cyclopropyloxyimino, cyclopentyloxyimino, cyclohexyloxyimino, and the like.

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The term "ethylenedioxy," as used herein, refers to a  $-OCH(R_{20})CH(R_{21})O-$  group wherein the oxygen atoms of the ethylenedioxy group are attached to the parent molecular moiety through one carbon atom forming a 5 membered ring or the oxygen atoms of the ethylenedioxy group are attached to the parent molecular moiety through two adjacent carbon atoms forming a six membered ring.  $R_{20}$  and  $R_{21}$  are independently selected from hydrogen and alkyl or  $R_{20}$  and  $R_{21}$  together with the carbon atoms to which they are attached can join to form a 5 or 6 membered ring optionally containing 1 heteroatom selected from NH, O, or S. Representative examples of ethylenedioxy include, but are not limited to, 3,5-dimethyl-1,2-cyclopentanediol, tetrahydro-3,4-furandiol, 1,2-cyclopentanediol, and the like.

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The term "formyl," as used herein, refers to a  $-C(O)H$  group.

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The term "formylalkyl," as used herein, refers to a formyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

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Representative examples of formylalkyl include, but are not limited to, formylmethyl, 2-formylethyl, and the like.

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

The term "haloalkoxy," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, pentafluoroethoxy, and the like.

The term "haloalkyl," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl, and the like.

The term "haloalkylcarbonyl," as used herein, refers to a haloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of haloalkylcarbonyl include, but are not limited to, 2-fluoroethylcarbonyl, trifluoromethylcarbonyl, pentafluoroethylcarbonyl, and the like.

The term "heterocycle" as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system. Monocyclic ring systems are exemplified by any 3- or 4-membered ring containing a heteroatom independently selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three heteroatoms wherein the heteroatoms are independently selected from nitrogen, oxygen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6- and 7-membered ring have from 0-3 double bonds.

Representative examples of monocyclic ring systems include, but are not limited to, azetidiny, azepiny, aziridiny, diazepiny, 1,3-dioxolany, dioxany, dithianyl, furyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolyl, isothiazolinyl, isothiazolidinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolyl, oxadiazolinyl, oxadiazolidinyl, oxazolyl, oxazolinyl, oxazolidinyl, piperaziny, piperidinyl, pyranly, pyrazinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, tetrahydrofurany, tetrahydrothiophenyl, tetrazinyl, tetrazolyl, thiadiazolyl, thiadiazolinyl, thiadiazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, thiophenyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, thiopyranly, triazinyl, triazolyl,

trithianyl, and the like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system. Bicyclic ring systems are further exemplified by any of the above monocyclic ring systems containing an alkylene of 1-3 carbon atoms attached to two non-adjacent carbon atoms of the monocyclic ring system. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazolyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzodioxinyl, 1,3-benzodioxolyl, cinnolinyl, hexahydro-1H-furo[3,4-c]pyrrolyl, indazolyl, indolyl, indolinyl, indoliziny, naphthyridinyl, isobenzofuranyl, isobenzothiophenyl, isoindolyl, isoindolinyl, isoquinolyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 1,4-dioxo-8-azaspiro[4.5]decanyl, 1,3-dioxo-8-azaspiro[4.5]decanyl, 1,5-dioxo-9-azaspiro[5.5]undecanyl, 1-oxa-4-thia-8-azaspiro[4.5]decanyl, 1-oxa-4,4-dioxo-4-thia-8-azaspiro[4.5]decanyl, 1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decanyl, phthalazinyl, pyranopyridyl, 2,4-(1H,3H)-quinazolin-3-yl, quinolyl, quinoliziny, quinoxaliny, quinazoliny, (3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-2-one, tetrahydroisoquinolyl, tetrahydroquinolyl, thiopyranopyridyl, and the like. Tricyclic ring systems are exemplified by any of the above bicyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or a monocyclic ring system. Representative examples of tricyclic ring systems include, but are not limited to, acridinyl, carbazolyl, carbolinyl, dibenzofuranyl, 2,4-(1H,3H)-quinazolin-1-one, dibenzothiophenyl, 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl, naphthofuranyl, naphthothiophenyl, oxanthrenyl, phenazinyl, phenoxathiinyl, phenoxazinyl, phenothiazinyl, thianthrenyl, thioxanthanyl, xanthanyl, and the like.

The heterocycles of this invention can be substituted with 1, 2, or 3 substituents independently selected from alkenyl, alkenyloxy, alkenyloxyimino, alkenyloxyiminoalkyl, alkoxy, alkoxyalkoxy, alkoxyalkoxyalkyl, alkoxyalkoxyimino, alkoxyalkyl, alkoxyalkynyl, alkoxyalkenyl, alkoxyalkynylalkenyl, alkoxyalkynylalkyl, alkoxyalkynylalkoxyimino, alkoxyalkynylalkoxyiminoalkyl, alkoxyimino, alkoxyiminoalkyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylcarbonyloxyalkoxy,

alkylcarbonyloxyalkyl, alkylcarbonyloxyalkylthio, alkylsulfonyl, alkylthio, alkylthioalkyl, aminoalkynyl, aminosulfonyl, azido, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, cycloalkylalkoxy, cycloalkylalkyl, cycloalkyloxy, cycloalkyloxyimino, ethylenedioxy, formyl, formylalkyl, haloalkyl, haloalkylcarbonyl, halogen, hydroxy, hydroxyalkoxy, hydroxyalkoxyalkyl, hydroxyalkyl, hydroxyimino, hydroxyiminoalkyl, methylenedioxy, methylenyl, nitro, oxo, phosphonato, spirocycle, (spirocycle)spirocycle, thioureylene, ureylene,  $-NZ_{12}Z_{13}$ ,  $(NZ_{12}Z_{13})$ alkyl,  $(NZ_{12}Z_{13})$ carbonyl, and  $(NZ_{12}Z_{13})$ carbonyloxy wherein  $Z_{12}$  and  $Z_{13}$  are independently selected from hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, alkylsulfonyl, aminoalkylcarbonyl, aminosulfonyl, aryl, arylalkyl, arylalkylcarbonyl, cyanoalkyl, cycloalkyl, cycloalkylalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, heterocyclesulfonyl, and  $(NZ_{14}Z_{15})$ alkyl wherein  $Z_{14}$  and  $Z_{15}$  are independently selected from the group consisting of hydrogen, alkoxyalkoxyalkyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkyl, alkylcarbonyl, formyl, heterocycle, and hydroxyalkoxyalkyl. Representative examples include, but are not limited to 4,4-(cis-1,2-dioxycyclopentyl)piperidinyl,

The term "heterocyclealkoxy," as used herein, refers to a heterocycle group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of heterocyclealkoxy include, but are not limited to, 2-pyrid-3-ylethoxy, 3-quinolin-3-ylpropoxy, 5-pyrid-4-ylpentyloxy, and the like.

The term "heterocyclealkoxyimino," as used herein, refers to a heterocyclealkoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of heterocyclealkoxyimino include, but are not limited to, 2-pyrid-3-ylethoxyimino, 3-quinolin-3-ylpropoxyimino, 5-pyrid-4-ylpentyloxyimino, 3-(4-morpholinyl)propoxyimino, and the like.

The term "heterocyclealkyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocyclealkyl include, but are not limited to, pyrid-3-ylmethyl, 2-pyrimidin-2-ylpropyl, and the like.

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The term "heterocyclealkylcarbonyl," as used herein, refers to a heterocyclealkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of heterocyclealkylcarbonyl include, but are not limited to, pyrid-3-ylmethylcarbonyl, 3-pyrimidin-2-ylpropylcarbonyl, and the like.

15

The term "(heterocycle)aryl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety a aryl group, as defined herein. Representative examples of (heterocycle)aryl include, but are not limited to, 4-(pyridin-3-yl)phenyl, 4-(pyrimidin-2-yl)phenyl, and the like.

20

10 The term "heterocyclecarbonyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of heterocyclecarbonyl include, but are not limited to, pyrid-3-ylcarbonyl, quinolin-3-ylcarbonyl, and the like.

25

15 The term "heterocycleimino," as used herein, refers to a heterocycle group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of heterocycleimino include, but are not limited to, 4-morpholinylimino, and the like.

30

20 The term "heterocycleoxy," as used herein, refers to a heterocycle group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of heterocycleoxy include, but are not limited to, pyrid-3-yloxy, quinolin-3-yloxy, and the like.

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25 The term "heterocycleoxyalkyl," as used herein, refers to a heterocycleoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocycleoxyalkyl include, but are not limited to, pyrid-3-yloxymethyl, 2-quinolin-3-yloxyethyl, and the like.

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The term "heterocycleoxyimino," as used herein, refers to a heterocycleoxy group, as defined herein, appended to the parent molecular moiety through an imino group, as defined herein. Representative examples of heterocycleoxyimino include, but are not limited to, pyrid-3-yloxyimino, quinolin-3-yloxyimino, and the like.

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The term "heterocycleoxyiminoalkyl," as used herein, refers to a heterocycleoxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocycleoxyiminoalkyl include, but are not limited to, 2-(pyrid-3-yloxyimino)ethyl, 2-(quinolin-3-yloxyimino)ethyl, and the like.

15

The term "heterocyclesulfonyl," as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of heterocyclesulfonyl include, but are not limited to, pyrid-3-ylsulfonyl, quinolin-3-ylsulfonyl, 4-morpholinylsulfonyl, and the like.

20

10 The term "hydroxy," as used herein, refers to an -OH group.

25

The term "hydroxyalkoxy," as used herein, refers to one or two hydroxy groups, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein. Representative examples of hydroxyalkoxy include, but are not limited to, 2-hydroxyethoxy, 2,3-dihydroxypropoxy, 4-hydroxybutoxy, and the like.

30

15 The term "hydroxyalkoxyalkyl," as used herein, refers to a hydroxyalkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkoxyalkyl include, but are not limited to, 2-[2-(hydroxy)ethoxy]ethyl, 2-[3-(hydroxy)propoxy]ethyl, 4-hydroxybutoxymethyl, and the like.

35

20 The term "hydroxyalkyl," as used herein, refers to one or two hydroxy groups, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, 2-hydroxyethyl, 2,3-dihydroxypropyl, and the like.

40

The term "hydroxyimino," as used herein, refers to a HON= group.

45

25 The term "hydroxyiminoalkyl," as used herein, refers to a hydroxyimino group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyiminoalkyl include, but are not limited to, 2-(hydroxyimino)ethyl, 3-(hydroxyimino)propyl, and the like.

50

The term "imino," as used herein, refers to a HN= group.

30 The term "mammal," has its ordinary meaning and includes human beings.

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The term "methylenedioxy," as used herein, refers to a  $-OCH_2O-$  group wherein the oxygen atoms of the methylenedioxy are attached to the parent molecular moiety through two adjacent carbon atoms forming a 5 membered ring. The carbon atom of methylenedioxy group is optionally substituted with one substituent selected from alkyl and oxo.

10

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The term "methylenyl," as used herein refers to a  $H_2C=$  group.

15

The term "nitro," as used herein, refers to a  $-NO_2$  group.

The term "oxo," as used herein, refers to a  $O=$  moiety.

The term "oxy," as used herein, refers to a  $-O-$  moiety.

10

The term "phosphonato," refers to a  $(R_{99}O)_2P(O)O-$  group wherein  $R_{99}$  is alkyl.

20

The term "spirocycle," as used herein, refers to a  $-X_1(CH_2)_pX_2-$  group wherein  $X_1$  and  $X_2$  are independently selected from  $CH_3$ ,  $NH$ ,  $O$ ,  $S$ ,  $S(O)$ , and  $S(O)_2$ ; and  $p$  is an integer from 2-3.  $X_1$  and  $X_2$  are attached to the parent molecular moiety through one carbon atom forming a 5 or 6 membered ring. Representative examples of spirocycle include, but are not limited to 1,3-dioxolane, 1,3-dioxane, 1,3-oxathiane, 1,3-oxazinane, and the like.

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The spirocycles of this invention are optionally substituted with 1, 2, or 3 substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, benzyloxycarbonyl, and formyl. The substituents can be attached to nitrogen or any of the carbon atoms.

30

20

The term "(spirocycle)spirocycle," as used herein, refers to a spirocycle, as defined herein, attached to the parent molecular moiety through a spirocycle, as defined herein. Representative examples of spirocycle-spirocycle include, but are not limited to, 1,7,9-trioxaspiro[4.5]decane, 1,4,7,9-tetraoxaspiro[4.5]decane, and the like.

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The term "thio," as used herein, refers to a  $-S-$  moiety.

The term "thioureylene," as used herein, refers to  $-NR_{97}C(S)NR_{98}R_{99}$ , wherein  $R_{97}$ ,  $R_{98}$ , and  $R_{99}$  are independently selected from hydrogen, alkyl, aryl, and arylalkyl, as defined herein.

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5 The term "ureylene," as used herein, refers to  $-NR_{97}C(O)NR_{98}R_{99}$ , wherein  $R_{97}$ ,  $R_{98}$ , and  $R_{99}$  are independently selected from hydrogen, alkyl, aryl, and arylalkyl, as defined herein.

10 In a further aspect of the present invention pharmaceutical compositions are disclosed which comprise a compound of the present invention in combination with a pharmaceutically acceptable carrier.

15 The present invention includes one or more compounds, as set forth above, formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively referred to herein as diluents, for parenteral injection, for oral administration in solid or liquid form, for rectal or topical administration, or the like. As is well known in the art, a compound of the present invention can exist in a variety of forms including pharmaceutically-acceptable salts, amides and the like.

20 Compositions may be prepared that will deliver the correct amount of a compound or compounds of the invention. The following dosages are thought to provide the optimal therapy: iv infusions: 0.1-250 nmol/kg/minute, preferably from 1-50 nmol/kg/minute; oral: 0.01-250  $\mu$ Mol/kg/day, preferably from about 0.1-50  $\mu$ Mol/kg/day; these oral molar dosage ranges correspond to 0.005-125 mg/kg/day, preferably 0.05-25 mg/kg/day. For treatment of acute disorders the preferred route of administration is intravenous; the preferred method of treating chronic disorders is orally by means of a tablet or sustained release formulation.

35 "Pharmaceutically-acceptable amide" refers to the pharmaceutically-acceptable, nontoxic amides of the compounds of the present invention which include amides formed with suitable organic acids or with amino acids, including short peptides consisting of from 1-to-6 amino acids joined by amide linkages which may be branched or linear, wherein the amino acids are selected independently from naturally-occurring amino acids, such as for example, glycine, alanine, leucine, valine, phenylalanine, proline, methionine, tryptophan, asparagine, aspartic acid, glutamic acid, glutamine, serine, threonine, lysine, arginine, tyrosine, histidine, ornithine, and the like.

5 "Pharmaceutically acceptable salts" refers to the pharmaceutically-acceptable, nontoxic, inorganic or organic acid addition salts of the compounds of the present invention, as described in greater detail below.

10 Compounds of the present invention can exist as stereoisomers wherein asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. 15 The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially 20 available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by 25 recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

30 The compounds of the present invention can be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, aspartate, 35 benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, flavianate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexonoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, 40 methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, succinate, tartrate, 25 thiocyanate, tosylate, and undecanoate.

45 Appropriate cationic salts are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of base, such as an alkali or alkaline earth metal hydroxide, e.g., sodium, potassium, lithium, calcium, or 30 magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine,

5 cyclohexylamine, dicyclohexylamine, triethylamine, piperidine, pyrrolidine, benzylamine,  
and the like, or a quaternary ammonium hydroxide such as tetramethylammonium  
hydroxide and the like. Also, the basic nitrogen-containing groups can be quaternized  
10 with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chlorides,  
5 bromides, and iodides; dialkyl sulfates; long chain halides such as decyl, lauryl, myristyl,  
and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl  
15 bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

The salts of the present invention can be synthesized from the compounds of  
Formula I which contain a basic or acidic moiety by conventional methods, such as by  
20 reacting the free base or acid with stoichiometric amounts or with an excess of the desired  
salt forming inorganic acid or base in a suitable solvent or various combinations of  
25 solvents.

Further included within the scope of the present invention are pharmaceutical  
25 compositions comprising one or more of the compounds of formula I prepared and  
15 formulated in combination with one or more non-toxic pharmaceutically acceptable  
carriers compositions, in the manner described below.

30 Compositions suitable for parenteral injection may comprise pharmaceutically  
acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions  
and sterile powders for reconstitution into sterile injectable solutions or dispersions.

20 Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles  
35 include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the  
like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic  
esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of  
40 a coating such as lecithin, by the maintenance of the required particle size in the case of  
25 dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting,  
45 emulsifying, and dispersing agents. Prevention of the action of microorganisms may be  
ensured by various antibacterial and antifungal agents, for example, parabens,  
chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include  
30 isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption

5 of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

10 If desired, and for more effective distribution, the compounds may be incorporated into slow-release or targeted-delivery systems, such as polymer matrices, liposomes, and  
5 microspheres. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid  
15 compositions, which may be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Solid dosage forms for oral administration may include capsules, tablets, pills,  
20 powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier), such as sodium citrate or dicalcium phosphate, and additionally (a) fillers or extenders, as for example, starches, lactose,  
25 sucrose, glucose, mannitol and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c)  
15 humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption  
30 accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin  
20 and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of  
35 capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and  
40 hard-filled gelatin capsules, using such excipients as lactose or milk sugar, as well as high  
25 molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills and granules may be prepared with coatings and shells, such as enteric coatings and others well known in this  
45 art. They may contain pacifying agents, and may also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a

5 delayed manner. Examples of embedding compositions which may be used are polymeric substances and waxes.

10 The active compounds may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

5 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, 15 such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed 20 oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

25 Besides such inert diluents, these liquid dosage forms may also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and 15 perfuming agents.

30 Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and 20 tragacanth, or mixtures of these substances, and the like.

35 Compositions for rectal or vaginal administrations are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and 40 therefore, melt in the rectum or vaginal cavity and release the active component.

45 Dosage forms for topical or transdermal administration of a compound of this invention further include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or transdermal patches. Transdermal administration via a transdermal patch is a particularly effective and preferred dosage form of the present invention. The 30 active component is admixed under sterile conditions with a pharmaceutically acceptable

5 carrier and any needed preservative, buffers or propellants as may be required. It is known  
that some agents may require special handling in the preparation of transdermal patch  
10 formulations. For example, compounds that are volatile in nature may require admixture  
with special formulating agents or with special packaging materials to assure proper  
5 dosage delivery. In addition, compounds which are very rapidly absorbed through the  
skin may require formulation with absorption-retarding agents or barriers. Ophthalmic  
15 formulations, eye ointments, powders and solutions are also contemplated as being within  
the scope of this invention.

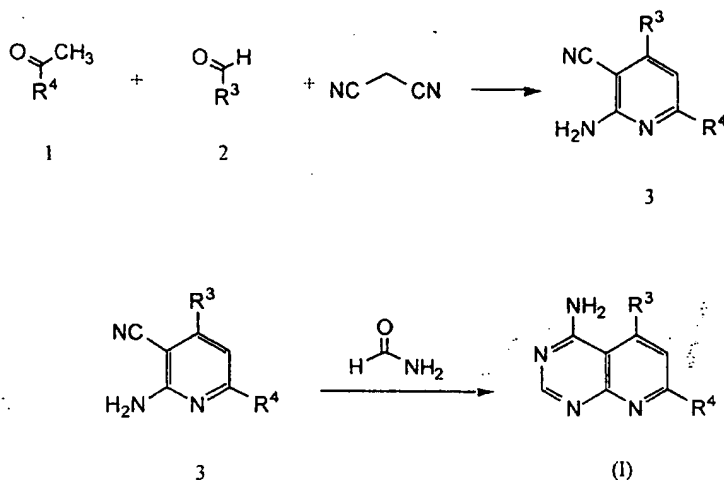
The present compounds may also be administered in the form of liposomes. As is  
10 known in the art, liposomes are generally derived from phospholipids or other lipid  
substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that  
20 are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and  
metabolizable lipid capable of forming liposomes may be used. The present compositions  
25 in liposome form may contain, in addition to the compounds of the present invention,  
15 stabilizers, preservatives, excipients, and the like. The preferred lipids are the  
phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.  
Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods  
30 in Cell Biology, Volume XIV, Academic Press, New York, N. Y., (1976), p 33 et seq.

#### 20 Synthetic Methods

35 The compounds and processes of the present invention will be better understood in  
connection with the following synthetic schemes which illustrate the methods by which  
the compounds of the invention may be prepared. The R groups are as defined above  
40 unless otherwise noted below.



Scheme 1



The compounds of the present invention may be synthesized by methods illustrated in Schemes 1 and 2. In accordance with Scheme 1, the 5,7-disubstituted compounds wherein  $R^4$  and  $R^3$  are aryl or a heterocyclic group may be prepared by a modification of a method of Kambe et al., *Synthesis*, 1980, 366-368. An appropriately substituted acetophenone (1, the " $R^4$  Reagent"), wherein  $R^4$  is aryl or a heterocyclic group, an appropriately substituted aldehyde (2, the " $R^3$  Reagent"),  $R^3$  is aryl or a heterocyclic group, and malononitrile are heated in the presence of ammonium acetate, or another suitable ammonium salt, such as for example, ammonium propionate, ammonium iodide, or the like, in an aprotic solvent to produce compound (3). The water of the reaction may be removed by use of a Dean Stark apparatus or by another suitable means, such as 4 Å molecular sieves. Suitable aprotic solvents include benzene, toluene, methylene chloride, DMF, THF, dioxane, and the like. The reaction may be performed at from about 40 °C to about 200 °C, and preferably at the reflux temperature of the solvent, for from about 1 hour to about 24 hours, preferably about 4 hours to 8 hours. The product (3) is preferably purified by chromatography after isolation from the reaction mixture. The above reaction may also proceed by contacting the aldehyde (2) with malononitrile and isolating the

5 resulting dicyano R<sup>3</sup> substituted alkene which is then reacted with the ketone (1) to form, upon addition of ammonium and cyclization, compound (3). Aliphatic aldehydes do not  
10 work effectively by this route. The ketone (1) may, however, include R<sup>4</sup> as alkyl groups.

15 The acetophenone starting materials (1) may be obtained commercially, or prepared easily by Friedel-Craft acylation of a suitable aromatic substrate, for example. The appropriate aldehyde starting materials (2) also may be obtained commercially, or  
20 may be prepared easily, for example by reductions of esters or acids with DIBAL or another suitable hydride reducing agent, or oxidation of alcohols under Swern conditions, for example.

25 Compound (3) is then treated with excess formamide by heating at reflux. The formation of product is monitored by TLC, and when the reaction is complete (after about 1 to about 8 hours) the reaction mixture is cooled to room temperature. The 5,7-disubstituted pyrido[2,3-d]pyrimidine product I is then removed by filtration and purified  
30 by column chromatography. This compound may then be partially or fully reduced by catalytic hydrogenation to the partially saturated or fully saturated version(s) (on the right side of the molecule) of the compounds shown in Scheme 1 or of Formula I.

35 Stereoisomers produced during these reduction steps are included within the scope of the invention. The present invention also contemplates reductions which produce single bonds between the 5,6 and 7,8 positions and a double bond between the 6,7 carbons. The  
40 stereoisomers may be isolated and purified by conventional means.

45 In accordance with Scheme 2 are prepared compounds of Formula I wherein R<sup>4</sup> is preferably an aryl, heterocycle or heterocyclic group, and R<sup>3</sup> is loweralkyl, loweralkenyl, loweralkynyl, or an arylalkyl group. In addition, R<sup>4</sup> may be selected from those additional groups listed in R<sup>3</sup>.

50 Compound (4, the "R<sup>3</sup> Reagent") may be obtained commercially or prepared from the precursor ester (5) or alcohol (5) by suitable reactions. Compound (5) may be reduced with a suitable reducing agent, such as for example, diisobutylaluminum hydride or  
55 another similar alkylaluminum hydride, under conditions well known to the art. Compound (6) may be oxidized to the aldehyde (4) Swern oxidation conditions, or other

5

reactions known to those skilled in the art. The desired compound (4) is freshly prepared before its use in the reaction described below.

10

Compound (9), the "R<sup>1</sup> Reagent" may be prepared from the precursor alpha-bromo ketone (7) by a two-step procedure. Compound (7) is treated with triphenylphosphine in the presence of a base, such as for example, triethyl amine, to give compound (8).

5

15

Compound (8) is then treated with an alkali metal base, such as NaOH or the like, to give compound (9). The procedure is normally accomplished by vigorous mixing of a solution of (8) in an organic solvent with an aqueous solution of base.

20

Compounds (4) and (9) are mixed and the mixture is held at ambient temperature until the reaction is complete (monitoring by TLC), and the product (10) is purified by chromatography. A mixture of the cis and trans isomers is obtained and taken to the next step without further separation. Compound (10) is condensed with malononitrile by heating in the presence of ammonium acetate as defined for Scheme 1 above to produce compound (11).

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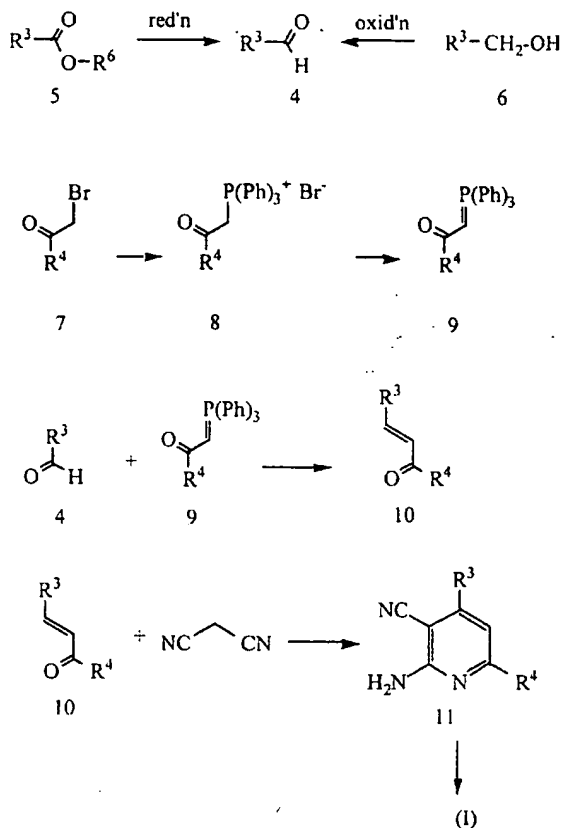
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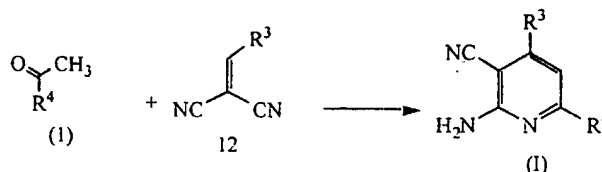
Scheme 2



Compound (11) is then treated with excess formamide by heating at reflux. The formation of product is monitored by TLC, and when the reaction is complete (routinely, after about 1 to about 8 hours) the reaction mixture is cooled to room temperature. The 5,7-disubstituted pyrido[2,3-d]pyrimidine product I is then removed by filtration and purified by column chromatography. In an alternate procedure, compound (11) is treated by heating with formamidine acetate in ethoxyethanol, followed by purification by flash chromatography. In another alternate procedure, compound (11) and ammonium sulfate

are heated at reflux in triethyl orthoformate for about 1 to about 8 hours, but preferably about 2 hours. The reaction mixture is cooled and added to a mixture of ammonia in ethanol. The mixture is stirred for about 12 to 24 hours at 25 °C, then at reflux for from one to 4 hours, and the solvent is removed in vacuo. The residue is purified by trituration with chloroform/ethyl acetate, and the product may be converted to a hydrochloride salt by suspension in 3M HCl, followed by lyophilization.

Scheme 3



Scheme 3 illustrates an alternate method for preparing the compounds I of the invention. Compounds (1), prepared as described above, are reacted with a dicyanoalkene compound (12) by heating with a suitable ammonium salt, such as for example, ammonium acetate, ammonium propionate, ammonium iodide, or the like, at reflux in an alcoholic or aprotic solvent to give the compound I. Suitable solvents for the reaction may be easily determined by those skilled in the art, without undue trial and error, and may include, for example, ethanol, propanol, isopropanol, t-butanol, n-butanol, 1,2-dichloroethane, benzene, chloroform, carbon tetrachloride, toluene, dioxane, dimethoxyethane, and the like. A preferred solvent is 1,2-dichloroethane. The dicyano compounds (12) may be prepared from the precursor aldehyde (4) by treatment with malononitrile in 1:1 H<sub>2</sub>O:EtOH in the presence of a catalytic amount of glycine according to the method of Bastus (Tetrahedron Lett., 1963: 955), or alternately MgO in dichloromethane or a similar aprotic solvent (cf. Broekhuis, et al., Recl. J. R. Neth. Chem. Soc., 99: 6-12 (1980); Moison, et al. Tetrahedron (1987), 43:537-542).

To prepare compounds of formula I wherein R<sup>1</sup> and R<sup>2</sup> are not both hydrogen atoms, it is possible to prepare the desired derivative from the compound of Formula I wherein R<sup>1</sup> and R<sup>2</sup> are both hydrogen atoms. When R<sup>1</sup> or R<sup>2</sup> is loweralkyl this may be

5 accomplished by reaction of the free amino group with the appropriate alkylating reagent, such as an alkyl halide, an alkyl mesylate or an alkyl tosylate, for example, in the presence of a base such as triethylamine or potassium carbonate in a suitable solvent, such as for  
10 example, methylene chloride or THF. When R<sup>1</sup> or R<sup>2</sup> is arylalkyl this may be accomplished by reaction of the free amino group with the appropriate arylalkyl halide, an alkyl mesylate or an alkyl tosylate, for example, in the presence of a base such as  
15 triethylamine or potassium carbonate in a suitable solvent, such as for example, methylene chloride or THF. When R<sup>1</sup> or R<sup>2</sup> is acyl this may be accomplished by reaction of the free amino group with the appropriate acid anhydride, acyl chloride or activated acyl group, in  
20 the presence of a base such as triethylamine or potassium carbonate in a suitable solvent, such as for example, methylene chloride or THF. When R<sup>1</sup> and R<sup>2</sup> are taken together with the nitrogen atom to which they are attached to form a 5-to-7 membered ring optionally containing an additional oxygen or nitrogen atom, the compound may be prepared by  
25 reacting a precursor compound having a halogen atom in place of the amino group at the 4-position with a 5-7 membered ring compound optionally containing an additional oxygen or nitrogen atom. Examples of such compounds include, but are not limited to, morpholine, piperidine, pyrrolidine, piperazine, thiomorpholine, and the like. Also, this  
30 alternate procedure may be used to prepare alkyl substituted amino compounds, for example by reacting the chloro compound with a mono- or disubstituted amine, such as for example, diethylamine, allyl amine, dibutylamine. This reaction takes place readily in  
35 a solvent such as methylene chloride, for example, in the presence of a tertiary amine. The precursor compound having a halogen atom in place of the amino group at the 4-position may be prepared by substitution of triethyl orthoformate for the formamide followed by chlorination of the ring by treatment with phosphorous oxychloride or thionyl chloride in  
40 the presence of DMF in Scheme 1 wherein compound (3) is converted to compound I.

#### Method of Inhibiting Kinase

45 In yet another aspect of the present invention a process of inhibiting adenosine kinase is disclosed. In accordance with that process, an adenosine kinase enzyme is  
30 exposed to an effective inhibiting amount of an adenosine kinase inhibitor compound of

5 the present invention. Means for determining an effective inhibiting amount are well known in the art.

10 The adenosine kinase to be inhibited can be located in vitro, in situ or in vivo. Where the adenosine kinase is located in vitro, adenosine kinase is contacted with the  
5 inhibitor compound, typically by adding the compound to an aqueous solution containing the enzyme, radiolabeled substrate adenosine, magnesium chloride and ATP. AK activity  
15 of cell supernatants was assayed radiometrically. Assays were carried out at ambient temperature in a final volume of 100  $\mu$ L. The reaction mixture contained 64 mM Tris HCl (pH 7.5), 0.2 mM  $MgCl_2$ , 1 mM ATP, 0.2  $\mu$ M U- $[^{14}C]$ -adenosine or  $[^3H]$ -adenosine and  
20 appropriate volumes of rat brain cytosol as a source of adenosine kinase. The reaction was terminated after 15 min by spotting 40  $\mu$ L of the reaction mixture onto disks of Whatman DE-81 anion exchange paper. DE-81 disks were then air-dried, washed for 10 minutes in  
25 2 mM ammonium formate, then rinsed successively with distilled water, methanol and acetone, and dried. DE-81 disks were then soaked for 5 minutes in 0.1N HCl/0.4 M KCl  
15 before addition of scintillation cocktail and counting by liquid scintillation counting. The enzyme can exist in intact cells or in isolated subcellular fractions containing the enzyme. The enzyme is then maintained in the presence of the inhibitor for a period of time and  
30 under suitable physiological conditions. Means for determining maintenance times are well known in the art and depend inter alia on the concentrations of enzyme and the  
20 physiological conditions. Suitable physiological conditions are those necessary to maintain adenosine kinase viability and include temperature, acidity, tonicity and the like.  
35 Inhibition of adenosine kinase can be performed, by example, according to standard procedures well known in the art (Yamada, et al., Comp. Biochem. Physiol., (1982), 71B, 367-372), hereby incorporated by reference.

40 25 In vitro adenosine kinase activity can be measured using any of the standard procedures well known in the art. By way of example, cells containing adenosine kinase, such as IMR-32 human neuroblastoma cells, are incubated in the presence and absence of  
45 an inhibitor. Inhibition is measured as the ability to inhibit phosphorylation of externally applied  $^{14}C$ -adenosine by these cells. The cells can be intact or broken. The specificity of  
30 adenosine kinase inhibitory activity is determined by studying the effects of inhibitors on

5 adenosine A<sub>1</sub>, A<sub>2A</sub>, and A<sub>3</sub> receptor binding, adenosine deaminase activity and adenosine transport.

10 Where the adenosine kinase is located in situ or in vivo, the inhibiting compound is typically administered to a fluid perfusing the tissue containing the enzyme. That fluid  
5 can be a naturally occurring fluid such as blood or plasma or an artificial fluid such as saline, Ringer's solution and the like.

15 Numerous animal models for studying adenosine kinase activity and the effects of inhibiting such activity are well known in the art. By way of example, adenosine kinase inhibitors have been reported to protect rodents (e.g., mice and rats) from experimentally-  
10 induced seizure activity (Zhang, G., Murray, T.F., J. Pharmacol. Exp. Ther., 1993, 264, 1415-1424; Murray, T.F., et al., Drug Dev. Res., 1993, 28, 410-415; Kowaluk, E. A., et al., Drug Dev. Res., 1996, 37, 190), hereby incorporated by reference. Other animal  
20 models of adenosine kinase activity have been described (See, e.g., Davies, et al., Biochem. Pharmacol., 1984, 33, 347-355; Keil, et al., Eur. J. Pharmacol., 1994, 271, 37-  
25 46; Murray, et al., Drug Development Res., 1993, 28, 410-415), hereby incorporated by reference.

30 A method of inhibiting adenosine kinase in vivo is particularly useful in mammals such as humans. Administering a therapeutic amount of an inhibitor compound is typically accomplished by the parenteral (e.g., intravenous injection) or oral administration  
20 of the compound.

35 By a "therapeutically-effective amount" of the compound of the invention is meant a sufficient amount of the compound to treat adenosine kinase related disorders or those conditions or diseases which are ameliorated or modified by local inhibition of the enzyme which results in an increase in the concentration of adenosine. It will be understood,  
40 however, that the total daily usage of the compounds and compositions of the present invention is to be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will  
45 depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition  
30 employed; the age, body weight, general health, gender and diet of the patient; the time of



administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with specific compound employed; and the like factors well known in the medical arts and well within the capabilities of attending physicians.

The compounds of the invention were tested in vivo in the hot plate test of analgesia in mammals such as mice. For example, the compounds of examples 6, 79, 104, 130, 133, 134, 137, 205, 246 and 256 in the procedure described directly below were tested thirty minutes after pretreatment with the drugs (30  $\mu$ mol/kg i.p.) for latency to 10th jump (in seconds). The longer the number of seconds, the more effective the drug at masking the pain felt from the hot plate. Compound 6 resulted in 152 seconds relative to the vehicle alone of  $72.8 \pm 10.5$  seconds (average  $\pm$  standard deviation); compound 79 resulted in 143 seconds; compound 104 resulted in 180 seconds; compound 130 resulted in 158 seconds; compound 133 resulted in 131 seconds; compound 134 resulted in 137 seconds; compound 137 resulted in 159 seconds; compound 205 resulted in 158 seconds, compound 246 resulted in 160 seconds and compound 256 resulted in 143 seconds. Compounds of the invention are therefore potent pain relievers as demonstrated in this animal model.

#### Mouse Hot Plate Assay

Male CF1 mice (Charles River) of approximately 25-30 g body weight are pretreated with 10 ml/kg of the test compounds, i.p. or p.o, in groups of 8 animals per dose. At the end of the pretreatment period, the mice are placed in an Omnitech Electronics Automated 16 Animal Hot Plate Analgesia Monitor (Columbus, OH; Model AHP16AN) in individual, 9.8 x 7.2 x 15.3 cm (l x w x h) plastic enclosures on top of a copper plate warmed to 55 °C. Infrared sensors located near the top of each enclosure record beam crossings that occur as the mice jump off of the heated surface. Latency times for each jump are automatically recorded, and latency to both the first and tenth jumps are used for data analysis. Mice that do not reach the criteria of 10 jumps by 180 seconds are immediately removed from the hotplate to avoid tissue damage, and they are assigned the maximum value of 180 seconds as their latency to tenth jump.

Numerous other animal models of adenosine kinase activity have been described [See, e.g., Davies, et al., Biochem. Pharmacol., 33:347-355 (1984); Keil, et al., Eur. J. Pharmacol., 271:37-46 (1994); Murray, et al., Drug Development Res., 28:410-415 (1993)].

Compounds of the present invention were also tested in vitro. The results of some representative studies are shown below in Tables I below. The Examples provided before the claims are all adenosine kinase inhibitors. The data indicate that the compounds inhibit adenosine kinase and are useful as adenosine kinase inhibitors. The compounds of the invention including compounds of formula I and II with the variables recited herein are also useful as screening tools or as comparative indicators of adenosine kinase inhibition activity relative to unknown inhibitors or potential inhibitors.

Table I

Inhibition of Adenosine Kinase by Representative Compounds of the Invention

| Compound of Example No. | IC <sub>50</sub> (nM) |
|-------------------------|-----------------------|
| 6                       | 200                   |
| 15                      | 7                     |
| 44                      | 50                    |
| 53                      | 3                     |
| 56                      | 35                    |
| 57                      | 1                     |
| 64                      | 8                     |
| 79                      | 5                     |
| 81                      | 3                     |
| 100                     | 2                     |
| 104                     | 2                     |
| 130                     | 1                     |
| 133                     | 2                     |
| 134                     | 1                     |
| 137                     | 5                     |

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|     |      |
|-----|------|
| 147 | 150  |
| 150 | 150  |
| 170 | 1    |
| 175 | 300  |
| 177 | 25   |
| 201 | 3    |
| 205 | 3    |
| 208 | 4    |
| 246 | 5    |
| 247 | 3    |
| 256 | 1    |
| 270 | 20   |
| 272 | >100 |
| 274 | 2    |
| 283 | 8    |
| 288 | 0.3  |
| 290 | 1    |
| 291 | 0.6  |
| 292 | 10   |
| 303 | 1    |
| 304 | 1    |
| 306 | 0.3  |
| 308 | 2    |
| 309 | 0.1  |
| 315 | 0.3  |
| 319 | 1    |
| 327 | 1    |
| 330 | 5    |
| 333 | 2    |

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|     |     |
|-----|-----|
| 336 | 8   |
| 337 | 4   |
| 338 | 4.5 |
| 347 | 3   |
| 351 | 4   |
| 352 | 5   |
| 353 | 21  |
| 354 | 11  |
| 355 | 4   |
| 356 | 3   |
| 357 | 12  |
| 358 | 60  |
| 359 | 8   |
| 360 | 50  |
| 361 | 5   |
| 362 | 12  |
| 363 | 28  |
| 371 | 6   |
| 403 | 2   |
| 431 | 2   |
| 440 | 3   |
| 441 | 2   |
| 464 | 6   |
| 569 | 8   |

Additional compounds of the present invention were tested for adenosine kinase inhibition using the above protocol. These compounds exhibited potent inhibition of adenosine kinase with  $ED_{50}$ 's ranging from 1 to 500 nM.

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#### 5 Carrageenan hyperalgesia Test-Hotbox Assay

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This assay may be indicative of a compound's ability to produce analgesia against carrageenan and capsaicin induced hyperalgesia. The assay is further discussed in Hargreaves K, Dubner R, Brown F, Flores C, Joris J (1988), A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain 32: 77-88, hereby fully incorporated by reference.

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C/D Sprague Dawley rats (Charles River), body weight range 250-350 g, are acclimated in the test room for 30-60 min. before any treatment (habituation). Carrageenan (CARR)(lambda, from Sigma, St. Louis, MO) is dissolved in heated saline at 10 mg/ml. This solution is sonicated and vortexed and then cooled to room temperature. After rats have been habituated they are injected with 100 µl of the CARR solution into the plantar surface (s.c.) of the right hindpaw. A 26 3/8 g needle is used for injection. The insertion of the needle will start at the midline of the foot between the tori and project toward the heel ~0.25 cm. Needle is then slowly removed from the skin to prevent seepage. Test compounds are administered at a time predetermined in relation to CARR injection (typically 1 hour pre CARR administration). The left hindpaw receives no injections. After carrageenan injection the rats are returned to their cages until 30 minutes before testing at which time they are placed in the Hargreaves thermal stimulator apparatus (Hotbox) for a 30 minute habituation period. Testing (thermal stimulation) is then performed. Each rat is tested 3 times (both right and left hindpaw) with approx. 5 minute between trials. The standard setting for the thermal stimulator (voltmeter) is 4.5 and the maximum time of exposure is 20.48 seconds. Scoring is based on latency to withdrawal from the thermal stimuli (0-20.48 seconds) The 2 lowest times of the three taken are averaged and the means are then determined for both the right and left paws (n=6 in most cases). Data is analyzed using GB Stat, with ANOVA protected T-tests to determine significant carrageenan effect (right versus left in same animal) and analgesic effect (right drug treated vs. right control). Results are indicated below as ED<sub>50</sub> values in micromolar concentration. For those values in nanomolar concentration, the values are designated by "nm".

| 30 | <u>Compound</u> | <u>ED<sub>50</sub> value (micromole/kg)</u> |
|----|-----------------|---|
|----|-----------------|---|

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55

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Example 134 0.6

Example 351 3

Example 352 3

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Example 353 3

5 Example 354 1

Example 355 1

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Example 356 1

Example 357 3

Example 359 1

10 Example 534 3

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Additional compounds of the present invention were tested in the carrageenan and capsaicin induced hyperalgesia hotbox assay using the above protocol in C/D Sprague Dawley rats. These compounds exhibited ED<sub>50</sub>'s ranging from 1 to >10 micromolar.

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Compounds exhibiting less potency in the carrageenan hyperalgesia hotbox assay may

15 require a higher dose or potency may be species dependent.

#### Method of Treating Cerebral Ischemia, Epilepsy,

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Nociperception (Nociception) (Pain), Inflammation including conditions such as Septic Shock due to Sepsis Infection.

20 In yet another aspect of the present invention a method of treating cerebral ischemia, epilepsy, nociperception or nociception, inflammation including conditions such as septic shock due to sepsis infection in a human or lower mammal is disclosed, comprising administering to the mammal a therapeutically effective amount of a compound of formula I with R<sup>1</sup>-R<sup>4</sup> as defined herein. The preferred compounds are those

35 of formula II with the R variables as defined previously. In particular, the present invention relates to a method of treating the above disorders comprising administering a compound of formula II wherein R<sup>1</sup> is a substituted aryl or heterocycle moiety wherein the substituent (preferably halogen) is at the meta or 3-position relative to the ring attachment

40 and R<sup>4</sup> is a substituted heterocycle or aryl moiety wherein the substituent is at the para or

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4-position relative to the ring attachment. The most preferred use is in the treatment of pain.

Alterations in cellular adenosine kinase activity have been observed in certain disorders. Adenosine kinase activity was found to be decreased, relative to normal liver, in a variety of rat hepatomas: activity of the enzyme giving a negative correlation with tumor growth rate (Jackson, et al., Br. J. Cancer, 1978, 37: 701-713). Adenosine kinase activity was also diminished in regenerating liver after partial hepatectomy in experimental animals (Jackson, et al., Br. J. Cancer, 1978, 37: 701-713). Erythrocyte Adenosine kinase activity was found to be diminished in patients with gout (Nishizawa, et al., Clin. Chim. Acta 1976, 67: 15-20). Lymphocyte adenosine kinase activity was decreased in patients infected with the human immunodeficiency virus (HIV) exhibiting symptoms of AIDS, and increased in asymptomatic HIV-seropositive and HIV-seronegative high-risk subjects, compared to normal healthy controls (Renouf, et al., Clin. Chem. 1989, 35: 1478-1481). It has been suggested that measurement of adenosine kinase activity may prove useful in monitoring the clinical progress of patients with HIV infection (Renouf, et al., Clin. Chem. 1989, 35: 1478-1481). Sepsis infection may lead to a systemic inflammatory syndrome (SIRS), characterized by an increase in cytokine production, neutrophil accumulation, hemodynamic effects, and tissue damage or death. The ability of adenosine kinase inhibitor to elevate adenosine levels in tissues has been demonstrated to ameliorate syndrome symptoms, due to the known anti-inflammatory effects of adenosine. (Firestein, et al., J. of Immunology, 1994: 5853-5859). The ability of adenosine kinase inhibitors to elevate adenosine levels is expected to alleviate pain states, since it has been demonstrated that administration of adenosine or its analogs results in antinociception or antinociperception. (Swaynok, et al., Neuroscience, 1989, 32:557-569).

The following Examples illustrate preferred embodiments of the present invention and are not limiting of the specification and claims in any way.

#### Example 1

4-amino-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine

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A sample of 4-(4-bromophenyl)-3-cyano-6-(4-(dimethylamino)phenyl)pyridine-2-amine (1 g), was suspended in formamide (20 mL), and the reaction was heated to reflux. After about 3 hours, the reaction was complete as monitored by TLC, and the reaction mixture was cooled to room temperature. The product was allowed to precipitate, then recovered by filtration and washed with water. Additional product was recovered from the filtrate. The product was purified by column chromatography eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give the pure title compound. IR (KBr) 3503, 3398, 1731, 1658, 1510, 1467, 1278cm<sup>-1</sup>; MS m/z 421 (M+H)<sup>+</sup>.

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The 6-(4-bromophenyl)-3-cyano-4-(4-(dimethylamino)phenyl)pyridine-2-amine compound was prepared as follows:

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The reagents, 4-bromoacetophenone (10 mmol, the "R<sup>4</sup> reagent"), 4-dimethylaminobenzaldehyde (10 mmol, the "R<sup>3</sup> reagent"), malononitrile (10 mmol) and ammonium acetate (1.4 g) were added to 25 mL of benzene. The reaction mixture was heated to reflux in a vessel fitted with a Dean-Stork apparatus. After 3.5 hours, the mixture was cooled, and the solvent was removed. The residue was purified by flash chromatography, eluting with methylene chloride, with optional addition of 5% ethyl acetate to the eluant. MS m/z 394 (M+H)<sup>+</sup>.

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#### Examples 2-156

Following the procedures of Example 1, except substituting the appropriate reagents for R<sup>4</sup> and R<sup>3</sup> as indicated in Table 2 below, compounds of Examples 2-156 were prepared.



Table 2  
Examples 2-156

| Ex. No. | Name  | R <sup>4</sup> Reagent (for 7-position) | R <sup>3</sup> Reagent (for 5-position) | Analytical Data  |
|---------|---|---|---|--|
| 2       | 4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone      | 4-dimethylamino-benzaldehyde            | IR (KBr) 3440, 1615, 1760, 1210cm <sup>-1</sup> ; MS m/z 385 (M+H) <sup>+</sup> .              |
| 3       | 4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;       | 1-(4-dimethylaminophenyl)-ethanone      | 4-methoxybenzaldehyde                   | IR (KBr) 3330, 1600, 1640, 1780, 1200cm <sup>-1</sup> ; MS m/z 372(M+H) <sup>+</sup> .         |
| 4       | 4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;       | 1-(4-methoxyphenyl)-ethanone            | 4-dimethylamino-benzaldehyde            | IR (KBr) 3660, 1600, 1620, 1510, 1360, 1240 cm <sup>-1</sup> ; MS m/z 372 (M+H) <sup>+</sup> . |
| 5       | 4-amino-5-(4-isopropylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-methoxyphenyl)-ethanone            | 4-isopropyl-benzaldehyde                | IR (KBr) 3430, 3360, 1580, 1540 cm <sup>-1</sup> ; MS m/z 371 (M+H) <sup>+</sup> .             |

|    |  |  |                          |  |
|----|--|--|--------------------------|--|
| 6  | 4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;          | 1-(4-methoxyphenyl)-ethanone             | 4-neopentylbenzaldehyde  | IR (KBr) 3480, 2960, 1580, 1510, 1240 $\text{cm}^{-1}$ ; MS m/z 399 (M+H) <sup>+</sup> .       |
| 7  | 4-amino-5-(4-butoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;             | 1-(4-methoxyphenyl)-ethanone             | 4-butoxybenzaldehyde     | IR (KBr) 3480, 1600, 1580, 1510, 1240, 1180 $\text{cm}^{-1}$ ; MS m/z 401 (M+H) <sup>+</sup> . |
| 8  | 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;              | 1-(4-bromophenyl)-ethanone               | 4-methoxybenzaldehyde    | IR (KBr) 3660, 1600, 1680, 1520, 1240 $\text{cm}^{-1}$ ; MS m/z 407 (M+H) <sup>+</sup> .       |
| 9  | 4-amino-5-(4-isopropoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;         | 1-(4-methoxyphenyl)-ethanone             | 4-isopropoxybenzaldehyde | IR (KBr) 3480, 2940, 1600, 1580, 1504 $\text{cm}^{-1}$ ; MS m/z 386 (M+H) <sup>+</sup> .       |
| 10 | 4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine; | 1-(4-N-formylpiperazinylphenyl)-ethanone | 4-butoxybenzaldehyde     | IR (KBr) 3480, 2940, 1660, 1600, 1580, 1510 $\text{cm}^{-1}$ ; MS m/z 483 (M+H) <sup>+</sup> . |

|    |   |  |                          |  |
|----|---|--|--------------------------|--|
| 11 | 4-amino-5-(4-benzyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;             | 1-(4-methoxyphenyl)-ethanone                   | 4-benzyloxy-benzaldehyde | IR (KBr) 3480, 3040, 1600, 1580, 1560 cm <sup>-1</sup> ; MS m/z 435 (M+H) <sup>+</sup> .       |
| 12 | 4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;               | 1-(4-methoxyphenyl)-ethanone                   | 4-phenoxy-benzaldehyde   | IR (KBr) 3456, 3053, 1580, 1558, 1247 cm <sup>-1</sup> ; MS m/z 421 (M+H) <sup>+</sup> .       |
| 13 | 4-amino-5-(4-isopropylphenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(3-(diethylmalonyl)allyl)phenyl)-ethanone | 4-isopropyl-benzaldehyde | IR (KBr) 3480, 2980, 1735, 1580, 1555 cm <sup>-1</sup> ; MS m/z 539 (M+H) <sup>+</sup> .       |
| 14 | 4-amino-5-(4-isopropylphenyl)-7-(4-t-butylacrylphenyl)pyrido[2,3-d]pyrimidine;        | 1-(4-t-butylacrylphenyl)-ethanone              | 4-isopropyl-benzaldehyde | IR (KBr) 3471, 2957, 1708, 1584, 1556, 1149 cm <sup>-1</sup> ; MS m/z 467 (M+H) <sup>+</sup> . |
| 15 | 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-dimethylaminophenyl)-ethanone             | 3-bromo-benzaldehyde     | IR (KBr) 3480, 1610, 1580, 1560, 1360, 1200 cm <sup>-1</sup> ; MS m/z 421 (M+H) <sup>+</sup> . |

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| 16 | 4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-dimethylaminophenyl)-ethanone | 3,4-dimethoxybenzaldehyde                             | IR (KBr) 3450, 1610, 1580, 1560, 1510 $\text{cm}^{-1}$ ; MS $m/z$ 402 (M+H) <sup>+</sup> .             |
| 17 | 4-amino-5-(3- <i>t</i> -butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-(3-formylphenyl)acrylic acid <i>t</i> -butyl ester  | IR (KBr) 3480, 3400, 1700, 1610, 1580, 1560 $\text{cm}^{-1}$ ; MS $m/z$ 468 (M+H) <sup>+</sup> .       |
| 18 | 4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;               | 1-(4-dimethylaminophenyl)-ethanone | 3-methoxybenzaldehyde                                 | IR (KBr) 3475, 1610, 1580, 1560, 1200 $\text{cm}^{-1}$ ; MS $m/z$ 372 (M+H) <sup>+</sup> .             |
| 19 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-dimethylaminophenyl)-ethanone | 3,5-dimethoxybenzaldehyde                             | IR (KBr) 3419, 1637, 1600, 1572, 1371, 1202 $\text{cm}^{-1}$ ; MS $m/z$ 402 (M+H) <sup>+</sup> .       |
| 20 | 4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;   | 1-(4-dimethylaminophenyl)-ethanone | 2-[2-(3-formylphenyl)vinyl]malonic acid diethyl ester | IR (KBr) 3480, 1720, 1610, 1580, 1558, 1524, 1360 $\text{cm}^{-1}$ ; MS $m/z$ 540 (M+H) <sup>+</sup> . |

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| 21 | 4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;  | 1-(4-dimethylaminophenyl)-ethanone | 3-vinylpyridinyl-benzaldehyde  | IR (KBr) 3480, 1610, 1580, 1560, 1513, 1360 cm <sup>-1</sup> ; MS m/z 385 (M+H) <sup>+</sup> .       |
| 22 | 4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-trifluoromethyl-benzaldehyde | IR (KBr) 3480, 1610, 1580, 1560, 1360, 1200 cm <sup>-1</sup> ; MS m/z 410 (M+H) <sup>+</sup> .       |
| 23 | 4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;     | 1-(4-dimethylaminophenyl)-ethanone | 3-amido-benzaldehyde           | IR (KBr) 3480, 1610, 1580, 1380, 1200 cm <sup>-1</sup> ; MS m/z 446 (M+H) <sup>+</sup> .             |
| 24 | 4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-dimethylaminophenyl)-ethanone | 3-cyano-benzaldehyde           | IR (KBr) 3460, 3400, 2210, 1610, 1580, 1554, 1360 cm <sup>-1</sup> ; MS m/z 367 (M+H) <sup>+</sup> . |
| 25 | 4-amino-5-(3-benzyloxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;       | 1-(4-dimethylaminophenyl)-ethanone | 3-benzyloxy-benzaldehyde       | IR (KBr) 3470, 1640, 1580, 1550, 1515, 1357, 1250 cm <sup>-1</sup> ; MS m/z 448 (M+H) <sup>+</sup> . |

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| 26 | 4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-methoxyphenyl)-ethanone       | 3-methoxy-benzaldehyde     | IR (KBr) 3470, 1640, 1580, 1550, 1515, 1357, 1250, 1240, 1180 cm <sup>-1</sup> ; MS m/z 359 (M+H) <sup>+</sup> . |
| 27 | 4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine;              | 1-(4-butoxyphenyl)-ethanone        | 3-bromo-benzaldehyde       | IR (KBr) 3478, 1610, 1580, 1560, 1515, 1355, 1255, 1240, 1180 cm <sup>-1</sup> ; MS m/z 449 (M+H) <sup>+</sup> . |
| 28 | 4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-(2-pyridyl)-benzaldehyde | IR (microscope) 3476, 1609, 1580, 1560, 1358 cm <sup>-1</sup> ; MS m/z 419 (M+H) <sup>+</sup> .                  |
| 29 | 4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;      | 1-(4-dimethylaminophenyl)-ethanone | 3-methyl-benzaldehyde      | IR (microscope) 3400, 1640, 1600, 1580, 1540 cm <sup>-1</sup> ; MS m/z 356 (M+H) <sup>+</sup> .                  |

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| 30 | 4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-chloro-benzaldehyde  | IR (microscope)<br>3400, 1600,<br>1580, 1540 cm <sup>-1</sup> ;<br>MS m/z 376<br>(M+H) <sup>+</sup> .  |
| 31 | 4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-fluoro-benzaldehyde  | IR (microscope)<br>3480, 1640,<br>1580, 1560 cm <sup>-1</sup> ;<br>MS m/z 360<br>(M+H) <sup>+</sup> .  |
| 32 | 4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;        | 1-(4-methoxyphenyl)-ethanone       | 3-bromo-benzaldehyde   | IR (microscope)<br>3485, 1607,<br>1575, 1550,<br>1515, 1350,<br>1255, 1240,<br>1180, 1030 cm <sup>-1</sup> ;<br>MS m/z 407<br>(M+H) <sup>+</sup> . |
| 33 | 4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;        | 1-(4-bromophenyl)-ethanone         | 3-methoxy-benzaldehyde | IR (microscope)<br>3450, 1640,<br>1573, 1555,<br>1496, 1350,<br>1260 cm <sup>-1</sup> ; MS<br>m/z 407<br>(M+H) <sup>+</sup> .                      |

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| 34 | 4-amino-5-(3-bromophenyl)-7-phenylpyrido [2,3-d]pyrimidine;         | 1-phenyl-ethanone          | 3-bromo-benzaldehyde | IR (KBr) 3480, 1640, 1580, 1560, 1480, 1350, 700 cm <sup>-1</sup> ; MS m/z 377 (M+H) <sup>+</sup> .         |
| 35 | 4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine; | 1-(4-ethylphenyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope) 3480, 1645, 1580 (broad), 1490, 1380 cm <sup>-1</sup> ; MS m/z 405 (M+H) <sup>+</sup> .     |
| 36 | 4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-bromophenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3480, 1610, 1575, 1540, 1350 cm <sup>-1</sup> ; MS m/z 455 (M+H) <sup>+</sup> .                    |
| 37 | 4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-cyanophenyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope) 3480, 2230, 1618, 1580, 1555, 1545, 1350 cm <sup>-1</sup> ; MS m/z 402 (M+H) <sup>+</sup> . |



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| 38 | 4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine;                  | 1-(4-hydroxyphenyl)-ethanone       | 3-bromo-benzaldehyde            | IR (microscope)<br>3481, 3060<br>(broad), 1645,<br>1580, 1560,<br>1544, 1360,<br>1240 1155 cm <sup>-1</sup> ;<br>MS m/z 393<br>(M+H) <sup>+</sup> . |
| 39 | 4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;             | 1-(4-dimethylaminophenyl)-ethanone | 3-iodo-benzaldehyde             | IR (microscope)<br>3500, 3040,<br>1640, 1600,<br>1580, 1560 cm <sup>-1</sup> ;<br>MS m/z 468<br>(M+H) <sup>+</sup> .                                |
| 40 | 4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-dimethylaminophenyl)-ethanone | 3-ethoxy-benzaldehyde           | IR (microscope)<br>3460, 3250,<br>1640, 1600,<br>1580, 1560 cm <sup>-1</sup> ;<br>MS m/z 386<br>(M+H) <sup>+</sup> .                                |
| 41 | 4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-trifluoromethoxy-benzaldehyde | IR (microscope)<br>3480, 1710,<br>1610, 1580,<br>1560, 1540 cm <sup>-1</sup> ;<br>MS m/z 426<br>(M+H) <sup>+</sup> .                                |

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| 42 | 4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;     | 1-(4-dimethylaminophenyl)-ethanone | 3,5-dichlorobenzaldehyde     | IR (microscope) 3500, 3040, 1640, 1600, 1580, 1560 cm <sup>-1</sup> ; MS m/z 411 (M+H) <sup>+</sup> .            |
| 43 | 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-bromo-4-fluorobenzaldehyde | IR (microscope) 3440, 3015, 1633, 1607, 1583 cm <sup>-1</sup> ; MS m/z 438 (M+H) <sup>+</sup> .                  |
| 44 | 4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;        | 1-(4-dimethylaminophenyl)-ethanone | 3-hydroxybenzaldehyde        | IR (microscope) 3450, 1640, 1610, 1580, 1560 cm <sup>-1</sup> ; MS m/z 358 (M+H) <sup>+</sup> .                  |
| 45 | 4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;            | 1-(4-morpholinylphenyl)-ethanone   | 3-bromobenzaldehyde          | IR (microscope) 3483, 1607, 1578, 1561, 1518, 1355, 1228 1120 cm <sup>-1</sup> ; MS m/z 462 (M+H) <sup>+</sup> . |

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| 46 | 4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;     | 1-(4-piperidinylphenyl)-ethanone     | 3-bromo-benzaldehyde | IR (microscope) 3486, 1606, 1561, 1540, 1519, 1353, 1231, 1199, 1128 cm <sup>-1</sup> ; MS m/z 460 (M+H) <sup>+</sup> . |
| 47 | 4-amino-5-(3-bromophenyl)-7-(4-(imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(imidazol-1-yl)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3481, 1580, 1555, 1525, 1482, 1352, 1303, 1053 cm <sup>-1</sup> ; MS m/z 443 (M+H) <sup>+</sup> .              |
| 48 | 4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine;          | 1-(4-chlorophenyl)-ethanone          | 3-bromo-benzaldehyde | IR (KBr) 3470, 1635, 1580, 1560, 1500, 1350, 1090 cm <sup>-1</sup> ; MS m/z 411 (M+H) <sup>+</sup> .                    |
| 49 | 4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine;       | 1-(4-isopropylphenyl)-ethanone       | 3-bromo-benzaldehyde | IR (KBr) 3484, 1610, 1579, 1560, 1550, 1483, 1357 cm <sup>-1</sup> ; MS m/z 419 (M+H) <sup>+</sup> .                    |

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| 50 | 4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine;                 | 1-(4-trifluorophenyl)-ethanone      | 3-bromo-benzaldehyde             | IR (microscope) 3481, 3289, 1616, 1579, 1547, 1324, 1312, 1122, 1070 cm <sup>-1</sup> ; MS m/z 445 (M+H) <sup>+</sup> . |
| 51 | 4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;              | 1-(4-diethylaminophenyl)-ethanone   | 3-bromo-benzaldehyde             | IR (KBr) 3481, 1607, 1578, 1561, 1533, 1353, 1200, 1155 cm <sup>-1</sup> ; MS m/z 448 (M+H) <sup>+</sup> .              |
| 52 | 4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine;            | 1-(3,4,5-trimethoxyphenyl)-ethanone | 3-bromo-benzaldehyde             | IR (KBr) 3485, 1579, 1548, 1507, 1340, 1129 cm <sup>-1</sup> ; MS m/z 467 (M+H) <sup>+</sup> .                          |
| 53 | 4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone  | 3-(3-methoxybenzyl)-benzaldehyde | IR (KBr) 3425, 1613, 1580, 1558, 1537 cm <sup>-1</sup> ; MS m/z 478 (M+H) <sup>+</sup> .                                |

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| 54 | 4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;    | 1-(4-dimethylaminophenyl)-ethanone | 3-methoxyethoxybenzaldehyde    | IR (KBr) 3469, 1610, 1580, 1560, 1357 cm <sup>-1</sup> ; MS m/z 416 (M+H) <sup>+</sup> .                    |
| 55 | 4-amino-5-(3,4-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3,4-methylenedioxybenzaldehyde | IR (KBr) 3466, 16245, 1579, 1560 cm <sup>-1</sup> ; MS m/z 386 (M+H) <sup>+</sup> .                         |
| 56 | 4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine;                   | 1-(4-ethoxyphenyl)-ethanone        | 3-bromo-benzaldehyde           | IR (KBr) 3480, 1607, 1579, 1560, 1517, 1360, 1238, 1180 cm <sup>-1</sup> ; MS m/z 421 (M+H) <sup>+</sup> .  |
| 57 | 4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine;                     | 1-(2-thienyl)-ethanone             | 3-bromo-benzaldehyde           | IR (KBr) 3470, 1579, 1560, 1547, 1429, 1361 cm <sup>-1</sup> ; MS m/z 383 (M+H) <sup>+</sup> .              |
| 58 | 4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;                   | 1-(4-fluorophenyl)-ethanone        | 3-bromo-benzaldehyde           | IR (microscope) 3476, 1600, 1580, 1555, 1515, 1350, 1230 cm <sup>-1</sup> ; MS m/z 395 (M+H) <sup>+</sup> . |

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| 59 | 4-amino-5-(3-dimethylaminophenyl)-7-(4-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-dimethylaminobenzaldehyde  | IR (KBr) 3436, 1601, 1580, 1563, 1534, 1200 cm <sup>-1</sup> ; MS m/z 385 (M+H) <sup>+</sup> .             |
| 60 | 4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;                     | 1-(4-dimethylaminophenyl)-ethanone | benzaldehyde                 | IR (KBr) 3400, 1600, 1580, 1560, 1530, 1200 cm <sup>-1</sup> ; MS m/z 342 (M+H) <sup>+</sup> .             |
| 61 | 4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;   | 1-(4-dimethylaminophenyl)-ethanone | 3,4,5-trimethoxybenzaldehyde | IR (KBr) 33460, 1607, 1578, 1127cm <sup>-1</sup> ; MS m/z 432 (M+H) <sup>+</sup> .                         |
| 62 | 4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;                    | 1-(4-nitrophenyl)-ethanone         | 3-bromobenzaldehyde          | IR (microscope) 3485, 1618, 1580, 1550, 1520, 1340, 860 cm <sup>-1</sup> ; MS m/z 422 (M+H) <sup>+</sup> . |
| 63 | 4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;                     | 1-(4-iodophenyl)-ethanone          | 3-bromobenzaldehyde          | IR (KBr) 3480, 1610, 1575, 1570, 1540, 1350, 1000 cm <sup>-1</sup> ; MS m/z 503 (M+H) <sup>+</sup> .       |

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| 64 | 4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine; | 1-(3,4-methylenedioxyphenyl)-ethanone | 3-bromo-benzaldehyde       | IR (KBr) 3485, 1607, 1575, 1545, 1500, 1440, 1350, 1255, 1038 cm <sup>-1</sup> ; MS m/z 421 (M+H) <sup>+</sup> . |
| 65 | 4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyridine [2,3-d]pyrimidine;   | 1-(4-morpholinylphenyl)-ethanone      | thiophene-2-carboxaldehyde | IR (KBr) 3480, 1607, 1580; 1560, 1226 cm <sup>-1</sup> ; MS m/z 390 (M+H) <sup>+</sup> .                         |
| 66 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yl)pyrido[2,3-d]pyrimidine;      | 1-(thiophen-2-yl)-ethanone            | 3,5-dimethoxy-benzaldehyde | IR (KBr) 3450, 1640, 1600, 1580, 1560 cm <sup>-1</sup> ; MS m/z 365 (M+H) <sup>+</sup> .                         |
| 67 | 4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine;      | 1-(4-carboxamidophenyl)-ethanone      | 3-bromo-benzaldehyde       | IR (KBr) 3481, 1674, 1611, 1577, 1558, 1352 cm <sup>-1</sup> ; MS m/z 420 (M+H) <sup>+</sup> .                   |

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| 68 | 4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyethoxy)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(2-methoxyethoxy)phenyl)-ethanone | 3-bromo-benzaldehyde           | IR (KBr) 3478, 1607, 1580, 1560, 1515, 1357, 1260, 1235, 1180, 1113 cm <sup>-1</sup> ; MS m/z 451 (M+H) <sup>+</sup> . |
| 69 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine; | 1-(4-morpholinylphenyl)-ethanone       | 3,5-dimethoxy-benzaldehyde     | IR (KBr) 3450, 1608, 1580, 1555, 1541, 1230, 1210, 1160 cm <sup>-1</sup> ; MS m/z 444 (M+H) <sup>+</sup> .             |
| 70 | 4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;  | 1-(thiophene-2-yl)-ethanone            | 3-trifluoromethyl-benzaldehyde | IR (KBr) 3486, 1620, 1580, 1560, 1325, 1123 cm <sup>-1</sup> ; MS m/z 373 (M+H) <sup>+</sup> .                         |
| 71 | 4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;             | 1-(4-aminophenyl)-ethanone             | 3-bromo-benzaldehyde           | IR (KBr) 3450, 1632, 1605, 1580, 1365 cm <sup>-1</sup> ; MS m/z 393 (M+H) <sup>+</sup> .                               |



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| 72 | 4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido [2,3-d]pyrimidine;       | 1-(thiophene-2-yl)-ethanone           | 3-bromo-4-fluoro-benzaldehyde | IR (KBr) 3480, 1640, 1580, 1560, 1500cm <sup>-1</sup> ; MS m/z 401 (M+H) <sup>+</sup> .                          |
| 73 | 4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido [2,3-d]pyrimidine;            | 1-(2-furanyl)-ethanone                | 3-bromo-4-fluoro-benzaldehyde | IR (KBr) 3460, 1600, 1580, 1560, 1500cm <sup>-1</sup> ; MS m/z 385 (M+H) <sup>+</sup> .                          |
| 74 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;             | 1-(4-iodophenyl)-ethanone             | 3,5-dimethoxy-benzaldehyde    | IR (KBr) 3460, 1604, 1575, 1556, 1541, 1207, 1160 cm <sup>-1</sup> ; MS m/z 485 (M+H) <sup>+</sup> .             |
| 75 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine;       | 1-(4-imidazolylphenyl)-ethanone       | 3,5-dimethoxy-benzaldehyde    | IR (KBr) 3459, 1604, 1580, 1556, 1524, 1484, 1304, 1159, 1056 cm <sup>-1</sup> ; MS m/z 425 (M+H) <sup>+</sup> . |
| 76 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(thiophene-2-yl)phenyl)-ethanone | 3,5-dimethoxy-benzaldehyde    | IR (KBr) 3457, 1602, 1579, 1557, 1207, 1159 cm <sup>-1</sup> ; MS m/z 441 (M+H) <sup>+</sup> .                   |

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| 77 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine;     | 1-(4-(3-pyridyl)phenyl)-ethanone           | 3,5-dimethoxy-benzaldehyde        | IR (KBr) 3452, 1604, 1578, 1558, 1287, 1206, 1159 cm <sup>-1</sup> ; MS m/z 436 (M+H) <sup>+</sup> .            |
| 78 | 4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(4-methylpiperidinyl)phenyl)-ethanone | 3-bromo-benzaldehyde              | IR (KBr) 3475, 1607, 1577, 1558, 1540, 1356, 1232 cm <sup>-1</sup> ; MS m/z 475 (M+H) <sup>+</sup> .            |
| 79 | 4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;          | 1-(4-pyrrolidinylphenyl)-ethanone          | 3-bromo-benzaldehyde              | IR (KBr) 3486, 1608, 1577, 1560, 1533, 1353, 1196 cm <sup>-1</sup> ; MS m/z 446 (M+H) <sup>+</sup> .            |
| 80 | 4-amino-5-(4-bromothiophen-2-yl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;  | 1-(4-dimethylaminophenyl)-ethanone         | 4-bromothiophene-2-carboxaldehyde | IR (KBr) 3327, 1604, 1578, 1548, 1521, 1367, 1350, 1202, 820 cm <sup>-1</sup> ; MS m/z 426 (M+H) <sup>+</sup> . |

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| 81 | 4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-morpholinylphenyl)-ethanone   | 4-bromothiophene-2-carboxaldehyde     | IR (KBr) 3460, 1606, 1578, 1558, 1541, 1517, 1232, 824 $\text{cm}^{-1}$ ; MS $m/z$ 468 (M+H) <sup>+</sup> . |
| 82 | 4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-dimethylaminophenyl)-ethanone | 3-bromophenylbenzaldehyde             | IR (microscope) 3340, 1603, 1580, 1540 $\text{cm}^{-1}$ ; MS $m/z$ 490 (M+H) <sup>+</sup> .                 |
| 83 | 4-amino-5-(4-(5-bromothiophene-2-yl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine; | 1-(4-morpholinylphenyl)-ethanone   | 4-(5-bromothiophene-2-yl)benzaldehyde | IR (KBr) 3460, 1606, 1580, 1558, 1541, 1517, 1233 $\text{cm}^{-1}$ ; MS $m/z$ 468 (M+H) <sup>+</sup> .      |
| 84 | 4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;                 | 1-(4-dimethylaminophenyl)-ethanone | 4-bromobenzaldehyde                   | IR (microscope) 3480, 3320, 1603, 1580, 1540, 820 $\text{cm}^{-1}$ ; MS $m/z$ 420 (M+H) <sup>+</sup> .      |
| 85 | 4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine;                 | 1-(4-(acetylamino)phenyl)-ethanone | 3-bromobenzaldehyde                   | IR (microscope) 3480 1600, 1580, 1520 $\text{cm}^{-1}$ ; MS $m/z$ 434 (M+H) <sup>+</sup> .                  |

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| 86 | 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;                 | 1-(4-dimethylaminophenyl)-ethanone | 3-bromo-benzaldehyde              | IR (microscope) 3300, 1606, 1600, 1580, 1560 cm <sup>-1</sup> ; MS m/z 421 (M+H) <sup>+</sup> .                         |
| 87 | 4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-d]pyrimidine;             | 1-(5-pyrimidinylphenyl)-ethanone   | 3,5-dimethoxy-benzaldehyde        | IR (microscope) 3458, 1602, 1579, 1558; 1460, 1414, 1364, 1196, 1058 cm <sup>-1</sup> ; MS m/z 437 (M+H) <sup>+</sup> . |
| 88 | 4-(4-fluorophenylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-bromo-benzaldehyde              | IR (KBr) 3410, 1605, 1570, 1525, 1503 cm <sup>-1</sup> ; MS m/z 514 (M+H) <sup>+</sup> .                                |
| 89 | 4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;          | 1-(4-pyrrolidinylphenyl)-ethanone  | 4-bromothiophene-2-carboxaldehyde | IR (KBr) 3470, 1609, 1577, 1555, 1520, 1409, 1386, 1350, 1196, 821 cm <sup>-1</sup> ; MS m/z 452 (M+H) <sup>+</sup> .   |

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| 90 | 4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;                  | 1-(thiophene-2-yl)-ethanone                  | 4-bromothiophene-2-carboxaldehyde    | IR (KBr) 3308, 1606, 1578, 1543, 1526, 1427, 1359 cm <sup>-1</sup> ; MS m/z 389 (M+H) <sup>+</sup> .              |
| 91 | 4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-d]pyrimidine;         | 1-(5-(dimethylamino)thiophene-2-yl)-ethanone | 3-bromo-benzaldehyde                 | IR (microscope) 3490, 1581, 1556, 1501, 1481, 1407, 1373, 1072 cm <sup>-1</sup> ; MS m/z 426 (M+H) <sup>+</sup> . |
| 92 | 4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;          | 1-(4-(dimethylamino)phenyl)-ethanone         | 3-bromo-5-iodo-benzaldehyde          | IR (KBr) 3493, 1608, 1562, 1533, 1364, 1350, 1200 cm <sup>-1</sup> ; MS m/z 546 (M+H) <sup>+</sup> .              |
| 93 | 4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(dimethylamino)phenyl)-ethanone         | 3,5-di(trifluoromethyl)-benzaldehyde | IR (KBr) 3484, 1607, 1580, 1554, 1386, 1280 cm <sup>-1</sup> ; MS m/z 478 (M+H) <sup>+</sup> .                    |

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| 94 | 4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;   | 1-(4-morpholinylphenyl)-ethanone           | 3,5-di(trifluoromethyl)-benzaldehyde | IR (KBr) 3500, 1643, 1602, 1578, 1554, 1280 cm <sup>-1</sup> ; MS m/z 520 (M+H) <sup>+</sup> .                        |
| 95 | 4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-(dimethylamino)phenyl)-ethanone       | 3,5-dibromo-benzaldehyde             | IR (KBr) 3440, 1608, 1570, 1559, 1536 cm <sup>-1</sup> ; MS m/z 498 (M+H) <sup>+</sup> .                              |
| 96 | 4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;               | 1-(4-morpholinylphenyl)-ethanone           | 3,5-dibromo-benzaldehyde             | IR (KBr) 3480, 1607, 1560, 1540, 1225 cm <sup>-1</sup> ; MS m/z 540 (M+H) <sup>+</sup> .                              |
| 97 | 4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(4-methylpiperidinyl)phenyl)-ethanone | 4-bromothiophene-2-carboxaldehyde    | IR (KBr) 3460, 1608, 1576, 1557, 1540, 1513, 1384, 1353, 1240, 823 cm <sup>-1</sup> ; MS m/z 481 (M+H) <sup>+</sup> . |
| 98 | 4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-(dimethylamino)phenyl)-ethanone       | 3,5-dibromo-benzaldehyde             | IR (KBr) 3486, 1608, 1570, 1559, 1536, 1360, 1350, 1200, 823 cm <sup>-1</sup> ; MS m/z 498 (M+H) <sup>+</sup> .       |

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| 99  | 4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(dimethylamino)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3480, 1601, 1579, 1548, 1483, 1357 cm <sup>-1</sup> ; MS m/z 420 (M+H) <sup>+</sup> .            |
| 100 | 4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;  | 1-(4-methylsulfonylphenyl)-ethanone  | 3-bromo-benzaldehyde | IR (KBr) 3486, 1600, 1580, 1550, 1490 cm <sup>-1</sup> ; MS m/z 455 (M+H) <sup>+</sup> .                  |
| 101 | 4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine;         | 1-(3-methoxyphenyl)-ethanone         | 3-bromo-benzaldehyde | IR (KBr) 3486, 1605, 1578, 1550, 1492, 1346, 1263 cm <sup>-1</sup> ; MS m/z 407 (M+H) <sup>+</sup> .      |
| 102 | 4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine;    | 1-(4-(methylthio)phenyl)-ethanone    | 3-bromo-benzaldehyde | IR (KBr) 3485, 1607, 1578, 1566, 1538, 1350, 1094, 795 cm <sup>-1</sup> ; MS m/z 423 (M+H) <sup>+</sup> . |
| 103 | 4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine;      | 1-(3,4-dichlorophenyl)-ethanone      | 3-bromo-benzaldehyde | IR (KBr) 3482, 1634, 1576, 1545, 1488, 1342 cm <sup>-1</sup> ; MS m/z 445 (M+H) <sup>+</sup> .            |

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| 104 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(N-methyl-N-formylamino)phenyl)-ethanone | 3-bromo-benzaldehyde          | IR (KBr) 3478, 1672, 1639, 1603, 1579, 1547, 841 $\text{cm}^{-1}$ ; MS $m/z$ 434 (M+H) <sup>+</sup> .         |
| 105 | 4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine;              | 1-(4-methylaminophenyl)-ethanone              | 3-bromo-benzaldehyde          | IR (KBr) 3488, 1637, 1607, 1587, 1360 $\text{cm}^{-1}$ ; MS $m/z$ 480 (M+H) <sup>+</sup> .                    |
| 106 | 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;  | 1-(4-methylsulfonylphenyl)-ethanone           | 3-bromo-4-fluoro-benzaldehyde | IR (KBr) 3489, 1578, 1560, 1496, 1311, 1151, 775 $\text{cm}^{-1}$ ; MS $m/z$ 473 (M+H) <sup>+</sup> .         |
| 107 | 4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine;          | 1-(3-amino-4-methoxyphenyl)-ethanone          | 3-bromo-benzaldehyde          | IR (microscope) 3431, 1629, 1606, 1583, 1274 $\text{cm}^{-1}$ ; MS $m/z$ 422 (M+H) <sup>+</sup> .             |
| 108 | 4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;  | 1-(3-bromo-4-(dimethylamino)phenyl)-ethanone  | 3-bromo-benzaldehyde          | IR (microscope) 3470, 1638, 1570, 1560, 1538, 1480, 1345 $\text{cm}^{-1}$ ; MS $m/z$ 498 (M+H) <sup>+</sup> . |



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| 109 | 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;              | 1-(3-methyl-4-(dimethylamino)phenyl)-ethanone         | 3-bromo-benzaldehyde | IR (microscope) 3438, 1640, 1605, 1580, 1555, 1368 cm <sup>-1</sup> ; MS m/z 434 (M+H) <sup>+</sup> . |
| 110 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetylaminophenyl)pyrido[2,3-d]pyrimidine;      | 1-(4-(N-methyl-N-trifluoroacetylaminophenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3443, 1699, 1635, 1606, 1201 cm <sup>-1</sup> ; MS m/z 502 (M+H) <sup>+</sup> .              |
| 111 | 4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine;              | 1-(4-(dimethylamino)-3-fluorophenyl)-ethanone         | 3-bromo-benzaldehyde | IR (KBr) 3438, 1638, 1592, 1365 cm <sup>-1</sup> ; MS m/z 438 (M+H) <sup>+</sup> .                    |
| 112 | 4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylaminophenyl)pyrido[2,3-d]pyrimidine;                | 1-(4-(N-ethyl-N-formylaminophenyl)-ethanone           | 3-bromo-benzaldehyde | IR (KBr) 3477, 1672, 1604, 1580, 1562, 1353 cm <sup>-1</sup> ; MS m/z 448 (M+H) <sup>+</sup> .        |
| 113 | 4,4-bis(acetylamino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetylamino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(N-methyl-N-acetylamino)phenyl)-ethanone         | 3-bromo-benzaldehyde | IR (KBr) 3434, 1667, 1635, 1600, 1200 cm <sup>-1</sup> ; MS m/z 532 (M+H) <sup>+</sup> .              |

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| 114 | 4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-(N-acetyl-N-methylamino)phenyl)-ethanone         | 3-bromo-benzaldehyde | IR (KBr) 3443, 1667, 1635, 1600, 1200 $\text{cm}^{-1}$ ; MS $m/z$ 532 (M+H) <sup>+</sup> .              |
| 115 | 4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine;                     | 1-(4-(N-ethylamino)phenyl)-ethanone                   | 3-bromo-benzaldehyde | IR (KBr) 3441, 1633, 1603, 1572, 1368 $\text{cm}^{-1}$ ; MS $m/z$ 420 (M+H) <sup>+</sup> .              |
| 116 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(N-methyl-N-(2-methoxyethyl)amino)phenyl)-ethanone  | 3-bromo-benzaldehyde | IR (KBr) 3439, 1636, 1601, 1529, 1361 $\text{cm}^{-1}$ ; MS $m/z$ 464 (M+H) <sup>+</sup> .              |
| 117 | 4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;                 | 1-(N-isopropylamino)phenyl)-ethanone                  | 3-bromo-benzaldehyde | IR (KBr) 3430, 1632, 1600, 1578, 1530, 1357 $\text{cm}^{-1}$ ; MS $m/z$ 434 (M+H) <sup>+</sup> .        |
| 118 | 4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;   | 1-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope) 3488, 1657, 1604, 1579, 1552, 1118 $\text{cm}^{-1}$ ; MS $m/z$ 506 (M+H) <sup>+</sup> . |

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| 119 | 4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenylpyrido[2,3-d]pyrimidine; | 1-(4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3201, 1679, 1617, 1597, 1576, 1539, 1177, 1117 cm <sup>-1</sup> ; MS m/z 521 (M+H) <sup>+</sup> . |
| 120 | 4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenylpyrido[2,3-d]pyrimidine; | 1-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3475, 1681, 1579, 1351, cm <sup>-1</sup> ; MS m/z 491 (M+H) <sup>+</sup> .                        |
| 121 | 4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)amino)phenylpyrido[2,3-d]pyrimidine;          | 1-(4-N-(2-(dimethylamino)ethyl)amino)phenyl)-ethanone          | 3-bromo-benzaldehyde | IR (KBr) 3431, 1634, 1601, 1573, 1359 cm <sup>-1</sup> ; MS m/z 463 (M+H) <sup>+</sup> .                   |
| 122 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine;         | 1-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)-ethanone          | 3-bromo-benzaldehyde | IR (KBr) 3475, 2220, 1660, 1604, 1580, 1560, 1352 cm <sup>-1</sup> ; MS m/z 459 (M+H) <sup>+</sup> .       |
| 123 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine;   | 1-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)-ethanone    | 3-bromo-benzaldehyde | IR (KBr) 3475, 1663, 1604, 1578, 1559, 1352, 1114 cm <sup>-1</sup> ; MS m/z 478 (M+H) <sup>+</sup> .       |

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| 124 | 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;            | 1-(3-methyl-4-(N-formyl-N-methylamino)phenyl)-ethanone            | 3-bromo-benzaldehyde | IR (KBr) 3486, 1677, 1607, 1579, 1549, 1351 cm <sup>-1</sup> ; MS m/z 448 (M+H) <sup>+</sup> .              |
| 125 | 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;                     | 1-(3-methyl-4-(N-methylamino)phenyl)-ethanone                     | 3-bromo-benzaldehyde | IR (KBr) 3433, 1635, 1605, 1585, 1359 cm <sup>-1</sup> ; MS m/z 420 (M+H) <sup>+</sup> .                    |
| 126 | 4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine;                          | 1-(4-(4-methoxy-2-butyl)phenyl)-ethanone                          | 3-bromo-benzaldehyde | IR (microscope) 3473, 3063, 1710, 1671, 1582, 1564, 1352 cm <sup>-1</sup> ; MS m/z 593 (M+H) <sup>+</sup> . |
| 127 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope) 3443, 1638, 1606, 1582, 1359 cm <sup>-1</sup> ; MS m/z 463 (M+H) <sup>+</sup> .             |

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| 128 | 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope) 3484, 1701, 1610, 1579, 1559, 1221, 1205, 1151 cm <sup>-1</sup> ; MS m/z 516 (M+H) <sup>+</sup> . |
| 129 | 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;            | 1-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)-ethanone            | 3-bromo-benzaldehyde | IR (KBr) 3484, 1663, 1607, 1574, 1547, 1354 cm <sup>-1</sup> ; MS m/z 462 (M+H) <sup>+</sup> .                    |
| 130 | 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine;                          | 1-(6-dimethylamino-3-pyridinyl)-ethanone                          | 3-bromo-benzaldehyde | IR (KBr) 3428, 1652, 1635, 1606, 1585, 1365 cm <sup>-1</sup> ; MS m/z 421 (M+H) <sup>+</sup> .                    |
| 131 | 4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;                               | 1-(4-methylsulfonylphenyl)-ethanone                               | 3-cyano-benzaldehyde | IR (KBr) 3479, 1638, 1576, 1559, 1303, 1147 cm <sup>-1</sup> ; MS m/z 402 (M+H) <sup>+</sup> .                    |

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| 132 | 4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine;            | 1-(4-(N-methyl-N-formylamino)-phenyl)-ethanone            | 3-cyanobenzaldehyde | IR (KBr) 3418, 2230, 1688, 1674, 1584, 1554, 1114 cm <sup>-1</sup> ; MS m/z 381 (M+H) <sup>+</sup> . |
| 133 | 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;       | 1-(6-(N-methyl-N-formylamino)-3-pyridinyl)-ethanone       | 3-bromobenzaldehyde | IR (KBr) 3474, 1676, 1577, 1561, 1353, 1130 cm <sup>-1</sup> ; MS m/z 435 (M+H) <sup>+</sup> .       |
| 134 | 4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;                    | 1-(6-morpholinyl-3-pyridinyl)-ethanone                    | 3-bromobenzaldehyde | IR (KBr) 3487, 3396, 1601, 1580, 1558, 1234 cm <sup>-1</sup> ; MS m/z 463 (M+H) <sup>+</sup> .       |
| 135 | 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine; | 1-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)-ethanone | 3-bromobenzaldehyde | IR (KBr) 3476, 3307, 1702, 1683, 1605, 1560, 1116 cm <sup>-1</sup> ; MS m/z 465 (M+H) <sup>+</sup> . |
| 136 | 4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;                   | 1-(6-pyrrolidinyl-3-pyridinyl)-ethanone                   | 3-bromobenzaldehyde | IR (KBr) 3487, 3396, 1601, 1580, 1558, 1234 cm <sup>-1</sup> ; MS m/z 447 (M+H) <sup>+</sup> .       |

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|-----|--|---|----------------------|---|
| 137 | 4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;                | 1-(2-(dimethylamino)-5-pyrimidinyl)-ethanone                | 3-bromo-benzaldehyde | IR (microscope)<br>3442, 1640,<br>1604, 1577,<br>1536, 1408,<br>1367, 1348 cm <sup>-1</sup> ;<br>MS m/z 422<br>(M+H) <sup>+</sup> . |
| 138 | 4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine; | 1-(2-(N-methoxyethyl-N-methylamino)-5-pyrimidinyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope)<br>3439, 1640;<br>1606, 1587,<br>1556, 1537,<br>1374, 1347 cm <sup>-1</sup> ;<br>MS m/z 466<br>(M+H) <sup>+</sup> . |
| 139 | 4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;       | 1-(2-(N-formyl-N-methylamino)-5-pyrimidinyl)-ethanone       | 3-bromo-benzaldehyde | IR (microscope)<br>3472, 1687,<br>1583, 1565,<br>1459, 1353,<br>1142, 988 cm <sup>-1</sup> ;<br>MS m/z 436<br>(M+H) <sup>+</sup> .  |
| 140 | 4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;                | 1-(2-(N-methylamino)-5-pyrimidinyl)-ethanone                | 3-bromo-benzaldehyde | IR (microscope)<br>3483, 1605,<br>1550, 1346 cm <sup>-1</sup> ;<br>MS m/z 408<br>(M+H) <sup>+</sup> .                               |

|     |  |   |                      |   |
|-----|--|---|----------------------|---|
| 141 | 4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;     | 1-(2-pyrrolidinyl-5-pyrimidinyl)-ethanone         | 3-bromo-benzaldehyde | IR (KBr) 3468, 1600, 1581, 1552, 1527, 1482, 1330 cm <sup>-1</sup> ; MS m/z 448 (M+H) <sup>+</sup> .                          |
| 142 | 4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;      | 1-(2-morpholinyl-5-pyrimidinyl)-ethanone          | 3-bromo-benzaldehyde | IR (KBr) 3434, 1637, 1608, 1585, 1335, cm <sup>-1</sup> ; MS m/z 463 (M+H) <sup>+</sup> .                                     |
| 143 | 4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine; | 1-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)-ethanone | 3-bromo-benzaldehyde | IR (microscope) 3473, 1762, 1583, 1571, 1562, 1491, 1477, 1402, 1348, 1217 cm <sup>-1</sup> ; MS m/z 463 (M+H) <sup>+</sup> . |
| 144 | 4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine;                            | 1-(2-pyridyl)-ethanone                            | 3-bromo-benzaldehyde | IR (microscope) 3427, 3017, 1601, 783 cm <sup>-1</sup> ; MS m/z 351/353 (M+H) <sup>+</sup> .                                  |
| 145 | 4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine;                            | 1-(3-pyridyl)-ethanone                            | 3-bromo-benzaldehyde | IR (microscope) 3434, 3042, 1634, 1372 cm <sup>-1</sup> ; MS m/z 351/353 (M+H) <sup>+</sup> .                                 |



|     |   |                                    |                                  |   |
|-----|---|------------------------------------|----------------------------------|---|
| 146 | 4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;   | 1-(4-dimethylaminophenyl)-ethanone | 3-(thiophen-2-yl)-benzaldehyde   | IR (microscope) 3482, 2922, 1578, 1356 cm <sup>-1</sup> ; MS m/z 420/422 (M+H) <sup>+</sup> . |
| 147 | 4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;      | 1-(4-dimethylaminophenyl)-ethanone | 3-(furan-2-yl)-benzaldehyde      | IR (microscope) 3479, 3104, 1559, 1356 cm <sup>-1</sup> ; MS m/z 420/422 (M+H) <sup>+</sup> . |
| 148 | 4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine; | 1-(4-dimethylaminophenyl)-ethanone | 3-(3-methoxyphenyl)-benzaldehyde | IR (microscope) 3477, 2924, 1579, 1356 cm <sup>-1</sup> ; MS m/z 420/422 (M+H) <sup>+</sup> . |
| 149 | 4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;                      | 1-(4-dimethylaminophenyl)-ethanone | benzaldehyde                     | IR (microscope) 3477, 3298, 1580, 1355 cm <sup>-1</sup> ; MS m/z 315 (M+H) <sup>+</sup> .     |
| 150 | 4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;            | 1-(4-(morpholinyl)phenyl)-ethanone | 3-chloro-benzaldehyde            | IR (microscope) 3480, 3056, 1579, 1356 cm <sup>-1</sup> ; MS m/z 391 (M+H) <sup>+</sup> .     |
| 151 | 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;    | 1-(4-(morpholinyl)phenyl)-ethanone | 3-bromo-4-fluoro-benzaldehyde    | IR (microscope) 3491, 3044, 1560, 1230 cm <sup>-1</sup> ; MS m/z 453 (M+H) <sup>+</sup> .     |

|     |  |                                      |                                   |  |
|-----|--|--------------------------------------|-----------------------------------|--|
| 152 | 4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;            | 1-(4-iodophenyl)-ethanone            | 3-chloro-benzaldehyde             | IR (microscope) 3478, 3280, 1539, 1350 cm <sup>-1</sup> ; MS m/z 432 (M+H) <sup>+</sup> .                  |
| 153 | 4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(thiophen-2-yl)phenyl)-ethanone | 3-chloro-benzaldehyde             | IR (microscope) 3484, 3055, 1560, 1354 cm <sup>-1</sup> ; MS m/z 459 (M+H) <sup>+</sup> .                  |
| 154 | 4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(5-pyrimidinyl)phenyl)-ethanone | 3-chloro-benzaldehyde             | IR (microscope) 3477, 3040, 1578, 1351 cm <sup>-1</sup> ; MS m/z 459 (M+H) <sup>+</sup> .                  |
| 155 | 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;    | 1-(4-iodophenyl)-ethanone            | 3-bromo-4-fluoro-benzaldehyde     | IR (microscope) 3444, 3048, 1607, 1356 cm <sup>-1</sup> ; MS m/z 494/496 (M+H) <sup>+</sup> .              |
| 156 | 4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;  | 1-(4-methoxyphenyl)-ethanone         | 4-bromothiophene-2-carboxaldehyde | IR (microscope) 3460, 3300, 2900-3100, 1700, 1580, 1510 cm <sup>-1</sup> ; MS m/z 413 (M+H) <sup>+</sup> . |

Example 157

4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine  
hydrochloride

A mixture of 3-cyano-4-(3-bromophenyl)methyl-6-(4-(dimethylaminophenyl)pyridine-2-amine (1.58 g) and ammonium sulfate (40 mg) in triethyl orthoformate was heated at reflux for 2 hours. The reaction mixture was cooled and added to a mixture of 8 g of ammonia in 150 mL of ethanol. After 16 hours at 25 °C, the reaction was heated at reflux for two hours, and the solvent was removed in vacuo. The residue was purified by chromatography, then converted to the hydrochloride salt by treatment with ether/HCl, followed by drying to give the title compound.

The 3-cyano-4-(3-bromophenyl)methyl-6-(4-(dimethylaminophenyl)pyridine-2-amine was prepared by a four-step procedure as follows:

step 157a: preparation of 3-bromophenylacetaldehyde (the "R<sup>3</sup> reagent")

To a solution of ethyl 3-bromophenylacetate (10.2 g, US patent 2,624,731 (1950)) in 230 mL of dichloromethane was added 42 mL of 1M Dibal-H in toluene at -78 °C with stirring. After 40 minutes at -78 °C, 10 mL of methanol was added, and the reaction allowed to warm to room temperature and partitioned between 50 mL of dichloromethane and 1200 mL of saturated aqueous potassium sodium tartrate. The organic layer was dried over sodium sulfate and the aldehyde used immediately in the next step without purification.

step 157b: preparation of  $\alpha$ -(triphenylphosphonium)-4-(dimethylamino)phenylethan-1-one chloride

Following the procedure of Fukui et al. (J. Org. Chem. 33: 3594-3507 (1968)),  $\alpha$ -bromo-(4-dimethylaminophenyl)ethan-1-one (the "R<sup>4</sup> reagent", CAS #37904-72-6; Chem. Abst. (1956), 864) was treated with triphenylphosphine in triethylamine and acetonitrile. The  $\alpha$ -bromo-(4-dimethylaminophenyl)ethan-1-one was prepared by bromination with bromine in hydrobromic acid according to the method of Suzuki et al (J. Pharm. Soc.

Japan. (1955), 75:54. Removal of solvent and recrystallization from methanol/ethyl acetate/toluene gave the title product as a white powder.

step 157c: preparation of 1-(4-(dimethylamino)phenyl)-4-(3-bromophenyl)-but-2-en-1-one

20 g of  $\alpha$ -(triphenylphosphonium)-4-(dimethylamino)phenylethan-1-one chloride (from step b) was partitioned between dichloromethane and 50 mL of 2N NaOH. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was mixed with 3-bromophenylacetaldehyde (from step a) for 24 hours at 25 °C. The mixture was purified by chromatography to give 8.35 g (61%) of a cis/trans mixture of the title compound. The cis/trans mixture was taken to the next step without separation of the isomers.

step 157d: preparation of 3-cyano-4-(3-bromophenyl)methyl-6-(4-(dimethylaminophenyl)pyridine-2-amine

A mixture of 1-(4-(dimethylamino)phenyl)-4-(3-bromophenyl)-but-2-en-1-one chloride (3.85 g, from step c), ammonium acetate (2.6 g) and malononitrile (739 mg) in 3 mL of dimethoxyethane and 22 mL of ethanol was heated at 115 °C for 5 hours, then cooled and worked up by partitioning between dichloromethane and water. The residue obtained on concentration of the organic phase was purified by flash chromatography to give the title compound.

Examples 158-174

Following the procedures of Example 157, except substituting the appropriate reagents for the R<sup>1</sup> and R<sup>3</sup> reagents of Example 157 as indicated in Table 3 below, compounds of Examples 158-174 were prepared. The treatment with aqueous HCl was omitted, and the free bases were obtained except as indicated.

In Examples 167-174, the formamide or formamidine acetate (added periodically until the reaction was complete) treatment was replaced by treatment with triethyl orthoformate at reflux in the presence of a catalytic amount of ammonium sulfate, followed by cooling to 25 °C and addition of excess ammonia in ethanol. After 24 hours,

the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichlorobenzene at 120-180 °C for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary (chloroform in methanol).

Table 3  
Examples 158-187

| Ex. No. | Name   | R <sup>4</sup> Reagent (for 7-position) | R <sup>3</sup> Reagent (for 5-position) | Analytical Data   |
|---------|--|---|---|---|
| 158     | 4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine  | 1-(4-diethylaminophenyl)-ethanone       | 3-phenyl-propionaldehyde                | IR (KBr) 3340,3240-2800,1600,1580,1540; H. Res. MS m/z 398.2343 (M+H) <sup>+</sup> .          |
| 159     | 4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine | 1-(4-diethylaminophenyl)-ethanone       | 3-methyl-butanaldehyde                  | IR (KBr) 3550,3410,3320,3240-2800,1605,1580,1560 H. Res. MS m/z 350.2357 (M+H) <sup>+</sup> . |
| 160     | 4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine          | 1-(4-diethylaminophenyl)-ethanone       | pentanaldehyde                          | IR (KBr) 3450,3300,3200-2800,1660,1610,1580,1540 H. Res. MS m/z 350.2354 (M+H) <sup>+</sup> . |

|     |   |                                    |   |   |
|-----|---|------------------------------------|---|---|
| 161 | 4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine          | 1-(4-diethylaminophenyl)-ethanone  | 4-(4-bromophenyl)-propionaldehyde         | IR (KBr) 3500,3300,3200-3000,1650,1615,1580 H. Res. MS m/z 478.1429 (M+H) <sup>+</sup> .      |
| 162 | 4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine                          | 1-(4-dimethylaminophenyl)-ethanone | pentanal                                  | IR (KBr) 3400,3350,3200-2900,1650,1620,1580,1570 H. Res. MS m/z 322.2032 (M+H) <sup>+</sup> . |
| 163 | 4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine        | 1-(4-dimethylaminophenyl)-ethanone | 3-cyanophenyl-acetaldehyde                | IR (KBr) 2850-3550,2220,1610,1580,1560,1540 MS m/z 381 (M+H) <sup>+</sup> .                   |
| 164 | 4-amino-5-(2-(N-carbobenzyloxy)aminoethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone | 3-(N-carbobenzyloxy)-aminopropionaldehyde | IR (KBr) 3000-3500,1710,1690,1650,1590 H. Res. MS m/z 443.2184 (M+H) <sup>+</sup> .           |
| 165 | 4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine                    | 1-(4-dimethylaminophenyl)-ethanone | cycloheptane-carboxaldehyde               | IR (KBr) 3500,3250,3100,2950,2850,1620,1575 H. Res. MS m/z 362.2349 (M+H) <sup>+</sup> .      |

|     |  |                                    |   |   |
|-----|--|------------------------------------|---|---|
| 166 | 4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenylmethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone | ** procedure of Example 173. using 3-thiophenylboronic acid | IR (KBr) 3200-3450, 2950-3100, 1605, 1580, 1550 H. Res. MS m/z 472.1363 (M+H) <sup>+</sup> .  |
| 167 | 4-amino-5-(pentyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine                                    | 1-(4-diethylaminophenyl)-ethanone  | hexanal   | IR (KBr) 3430, 3320, 3240-2800, 1580, 1560, 1540, 1350; mp. 211-214; MS m/z 364 (M+H) <sup>+</sup> ; H. Res. MS m/z 364.2506 (M+H) <sup>+</sup> . |
| 168 | 4-amino-5-hexyl-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine                                       | 1-(4-diethylaminophenyl)-ethanone  | heptanal  | IR (KBr) 3440, 3310, 3240-2800, 1580, 1560, 1540, 1350; mp. 215-217; MS m/z 378 (M+H) <sup>+</sup> ; H. Res. MS m/z 378.2654 (M+H) <sup>+</sup> . |

|     |  |                                    |                                   |  |
|-----|--|------------------------------------|-----------------------------------|--|
| 169 | 4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine  | 1-(4-diethylaminophenyl)-ethanone  | 3-(3-bromophenyl)-propionaldehyde | IR (KBr) 3640-3240, 3200-2800, 1580, 1555, 1535, 1345; mp. 201-202; MS m/z 476/478 (M+H) <sup>+</sup> ; H. Res. MS m/z 476.1448 (M+H) <sup>+</sup> . |
| 170 | 4-amino-5-(2-(2-bromophenyl)methyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine | 1-(4-diethylaminophenyl)-ethanone  | 2-(2-bromophenyl)-acetaldehyde    | IR (KBr) 3640-3240, 3240-2800, 1580, 1555, 1540, 1350; mp. 130-133; MS m/z 462/464 (M+H) <sup>+</sup> ; H. Res. MS m/z 462.1297 (M+H) <sup>+</sup> . |
| 171 | 4-amino-5-cyclopropyl-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine              | 1-(4-dimethylaminophenyl)-ethanone | cyclopropanecarboxaldehyde        | IR (KBr) 3490, 3290, 3240-2760, 1610, 1580, 1540, 1375; mp. 235-237; MS m/z 462/464 (M+H) <sup>+</sup> ;   |
| 172 | 4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine               | 1-(4-dimethylaminophenyl)-ethanone | cyclohexanecarboxaldehyde         | IR (KBr) 3640-3000, 2980-2760, 1610, 1580, 1540, 1345; mp. 231-234; MS m/z 462/464 (M+H) <sup>+</sup> ;  |



|     |   |                                    |   |  |
|-----|---|------------------------------------|---|--|
| 173 | 4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone | 2-(2-bromo-5-chlorophenyl)-acetaldehyde | IR (KBr) 3460.3220-2760.1610,1575.1535.1365; mp. 185-187; MS m/z 462/464 (M+H) <sup>+</sup> ;      |
| 174 | 4-amino-5-methyl-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine                           | 1-(4-dimethylaminophenyl)-ethanone | acetaldehyde                            | IR (KBr) 3640-3250,3250-2760,1610,1585,1560,1350; mp. 238-246; MS m/z 462/464 (M+H) <sup>+</sup> ; |

\* prepared from the compound of Example 157 by reaction with Pd(PPh<sub>3</sub>)<sub>4</sub> and zinc cyanide in DMF under Suzuki reaction conditions.

\*\* prepared from the compound of Example 173 by reaction with 2-thiopheneboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub> and aqueous sodium carbonate under Suzuki reaction conditions.

#### Examples 175-188

Following the procedures of Example 1, except substituting the appropriate reagents for the R<sup>4</sup> and R<sup>3</sup> reagents of Example 1 as indicated in Table 4 below, compounds of Examples 175-188 were prepared. The treatment with aqueous HCl was omitted, and the free bases were obtained except as indicated.

Table 4

#### Examples 175-188

| Ex. No. | Name | R <sup>4</sup> Reagent (for 7-position) | R <sup>3</sup> Reagent (for 5-position) | Analytical Data |
|---------|------|---|---|-----------------|
|---------|------|---|---|-----------------|

|     |  |                                    |  |   |
|-----|--|------------------------------------|--|---|
| 175 | 4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine         | 1-(4-dimethylaminophenyl)-ethanone | 2,3-methylenedioxybenzaldehyde         | IR (KBr) 3500-2500.1595,1580,1375; mp. 290-305;   |
| 176 | 4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone | 3-fluoro-5-trifluoromethylbenzaldehyde | IR (KBr) 3500,3440-3240,3200-2800,1610,1580,1560,1540,1370; mp. 293-296; MS m/z 428 (M+H) <sup>+</sup> ; H. Res. MS m/z 428.1509 (M+H) <sup>+</sup> .     |
| 177 | 4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine                    | 1-(4-dimethylaminophenyl)-ethanone | 2-bromo-benzaldehyde                   | IR (KBr) 3480,3440-3240,3200-2800,1610,1575,1555,1535,1355; mp. 261-263; MS m/z 420/422 (M+H) <sup>+</sup> ; H. Res. MS m/z 420.0823 (M+H) <sup>+</sup> . |

|     |  |                                    |  |  |
|-----|--|------------------------------------|--|--|
| 178 | 4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine               | 1-(4-dimethylaminophenyl)-ethanone | 3,5-dimethylbenzaldehyde               | IR (KBr)<br>3480,3440-<br>3240,3200-<br>2800,1610,1575,1555,1535,1360; mp.<br>284-286; MS m/z<br>370 (M+H) <sup>+</sup> ; H.<br>Res. MS m/z<br>370.2036 (M+H) <sup>+</sup> .     |
| 179 | 4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine               | 1-(4-dimethylaminophenyl)-ethanone | 3,4-dichlorobenzaldehyde               | IR (KBr)<br>3490,3440-<br>3240,3200-<br>2800,1610,1575,1560,1535,1355; mp.<br>288-291; MS m/z<br>410/412 (M+H) <sup>+</sup> ; H.<br>Res. MS m/z<br>410.0948 (M+H) <sup>+</sup> . |
| 180 | 4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone | 4-fluoro-3-trifluoromethylbenzaldehyde | IR (KBr)<br>3500,3440-<br>3240,3200-<br>2800,1610,1580,1560,1540,1505,1360; mp. 254-257; MS<br>m/z 428 (M+H) <sup>+</sup> ; H.<br>Res. MS m/z<br>428.1487 (M+H) <sup>+</sup> .   |

|     |  |                                   |                                |   |
|-----|--|-----------------------------------|--------------------------------|---|
| 181 | 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)-pyrido[2,3-d]pyrimidine  | 1-(4-morpholinylphenyl)-ethanone  | 3-bromo-5-methoxy-benzaldehyde | IR (KBr)<br>3470,3440-<br>3240,3200-<br>2800,1605,1580,1560; mp. 257-260; MS m/z 492/494 (M+H) <sup>+</sup> .       |
| 182 | 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine | 1-(4-pyrrolidinylphenyl)-ethanone | 3-bromo-5-methoxy-benzaldehyde | IR (KBr)<br>3470,3440-<br>3240,3200-<br>2800,1610,1580,1560,1540,1355; mp. 250; MS m/z 476/478 (M+H) <sup>+</sup> . |
| 183 | 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)-pyrido[2,3-d]pyrimidine  | 1-(4-piperidinylphenyl)-ethanone  | 3-bromo-5-methoxy-benzaldehyde | IR (KBr)<br>3470,3440-<br>3240,3200-<br>2800,1565; mp. 224-244; MS m/z 490/492 (M+H) <sup>+</sup> ;                 |

|     |   |                                    |                                |  |
|-----|---|------------------------------------|--------------------------------|--|
| 184 | 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone | 3-bromo-5-methoxy-benzaldehyde | IR (KBr)<br>3470,3420-<br>3240,3200-<br>2800,1610,1575,1555,1535,1355; mp.<br>262-266; MS m/z<br>450/452 (M+H) <sup>+</sup> ; H.<br>Res. MS m/z<br>450.0944 (M+H) <sup>+</sup> . |
| 185 | 4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine      | 1-(4-dimethylaminophenyl)-ethanone | 3-methylthio-benzaldehyde      | IR (KBr)<br>3460,3420-<br>3240,3200-<br>2800,1605,1575,1560,1535,1355; mp.<br>184-220; MS m/z<br>388 (M+H) <sup>+</sup> ; H.<br>Res. MS m/z<br>388.1586 (M+H) <sup>+</sup> .     |
| 186 | 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)-pyrido[2,3-d]pyrimidine        | 1-(thiophene-2-yl)-ethanone        | 3-bromo-5-methoxy-benzaldehyde | IR (KBr)<br>3470,3350-<br>2200,1700,1640,1580,1435,1365,1270;<br>mp. 246-249; MS<br>m/z 413/415<br>(M+H) <sup>+</sup> ; H. Res.<br>MS m/z 413.0069<br>(M+H) <sup>+</sup> .       |

|     |   |                                    |                               |   |
|-----|---|------------------------------------|-------------------------------|---|
| 187 | 4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine *** | 1-(4-dimethylaminophenyl)-ethanone | 2,3-dimethoxy-benzaldehyde    | IR (KBr) 3480,3440-3240,3200-2800,1610,1580,1550,1530,1360; mp. 222-225; MS m/z 402 (M+H) <sup>+</sup> ; H. Res. MS m/z 402.1922 (M+H) <sup>+</sup> . |
| 188 | 4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine  | 1-(4-dimethylaminophenyl)-ethanone | 3-methylsulfonyl-benzaldehyde | IR (KBr) 3490,3400-2800,1610,1580,1555,1535,1355; mp. 245-270; MS m/z 420 (M+H) <sup>+</sup> ; H. Res. MS m/z 420.1493 (M+H) <sup>+</sup> .           |

Example 1894-acetyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

5 A suspension of 4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine (from Example 15, 0.28 g, 0.67 mole) in pyridine (3 mL) was treated with acetic anhydride (0.10 g, 1.0 mmol) and the reaction mixture was stirred for 4 hours at 25 °C. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO<sub>2</sub>, EtOAc/hexanes) to provide the title compound (0.23 g, 73% theoretical): IR (KBr) 3368, 3048, 1695, 1567; MS m/z 462/464 (M+H)<sup>+</sup>.

Examples 190-198

Following the procedures of Example 189, except substituting the appropriate acylating reagent for the acetic anhydride of Example 189 as indicated in Table 5 below, compounds of Examples 190-198 were prepared.

Table 5  
Examples 190-198

| Ex. No. | Name  | Acylating Reagent                | Analytical Data  |
|---------|---|----------------------------------|--|
| 190     | 4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine-190       | acetic anhydride and formic acid | IR (KBr) 3382, 3047, 1704, 1570; MS m/z 448/450 (M+H) <sup>+</sup> |
| 191     | 4-(methoxyacetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine   | methoxyacetyl chloride           | IR (KBr) 3344, 3044, 1731, 1561; MS m/z 492/494 (M+H) <sup>+</sup> |
| 192     | 4-trifluoroacetyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine | trifluoroacetic anhydride        | IR (KBr) 3426, 3072, 1610, 1578; MS m/z 516/518 (M+H) <sup>+</sup> |
| 193     | 4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine        | pentanoyl chloride               | IR (KBr) 3408, 2954, 1699, 1569; MS m/z 504/506 (M+H) <sup>+</sup> |
| 194     | 4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine          | benzoic anhydride                | IR (KBr) 3420, 3056, 1606, 1583; MS m/z 524/526 (M+H) <sup>+</sup> |

|     |   |                                |  |
|-----|---|--------------------------------|--|
| 195 | 4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine         | N-BOC-glycyl-imidazole         | IR (KBr) 3362, 2975, 1719, 1570; MS m/z 577/579 (M+H) <sup>+</sup> . |
| 196 | 4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine | N-phthalimidyl-glycyl-chloride | IR (KBr) 3408, 2927, 1719, 1570; MS m/z 607/609 (M+H) <sup>+</sup> . |
| 197 | 4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine       | diethyl dicarbonate            | IR (KBr) 3405, 2987, 1738, 1569; MS m/z 492/494 (M+H) <sup>+</sup> . |
| 198 | 4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)-pyrido[2,3-d]pyrimidine   | ethyl isocyanate               | IR (KBr) 3405, 3053, 1701, 1548; MS m/z 491/493 (M+H) <sup>+</sup> . |

Example 1994-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

The product was prepared by treating a solution of 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine in CH<sub>2</sub>Cl<sub>2</sub>-TEA with allylamine and heating the resulting mixture at reflux for 1 hour. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO<sub>2</sub>, EtOAc/hexanes) to provide the title compound IR (KBr) 3437, 1564, 1355, 1195; MS m/z 460/462 (M+H)<sup>+</sup>.

The 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine was prepared as follows.

A sample of 4-(4-bromophenyl)-3-cyano-6-(4-(dimethylamino)phenyl)pyridine-2-amine (from Example 1, 5.0 g, 12.7 mmol) in 20 mL of H<sub>2</sub>SO<sub>4</sub> was heated at 80 °C for 30



minutes. Ice was added, and the reaction mixture was neutralized with aqueous NaOH. The resulting crude 3-carboxamide was collected by filtration, triturated with EtOAc-hexanes, then dried under reduced pressure (4.95 g, 95% theoretical). A solution of the carboxamide (4.25 g, 10.3 mmol) in triethylorthoformate (20 mL) was treated with p-toluenesulfonic acid (catalytic) and the reaction mixture was warmed at 80 °C for 4 hours. The volatiles were removed and the crude bicyclic 4-hydroxyl-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine product was suspended in POCl<sub>3</sub> (15 mL) then warmed at 100 °C for 2 hours. The POCl<sub>3</sub> was removed under reduced pressure to provide crude 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine. The invention therefore relates to intermediate compounds of formula III wherein X is selected from hydroxyl or halogen and the remaining variables are the same as in formula I or II.

#### Example 200

4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido [2,3-d] pyrimidine trihydrochloride

The product was prepared by treating a solution of 4-chloro-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine (prepared as in Example 199) in CH<sub>2</sub>Cl<sub>2</sub>-TEA with the 2-(dimethylamino)ethylamine and heating the resulting mixture at reflux for 1 hour. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO<sub>2</sub>, EtOAc/hexanes) to provide the title compound. The product was treated with excess 2M HCl (aq) followed by lyophilization to give the product as the trihydrochloride salt; IR (KBr) 3385, 1561, 1356, 1197; MS m/z 491/493 (M+H)<sup>+</sup>.

#### Example 201

4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl) pyrido [2,3-d] pyrimidine tetrahydrochloride

The product was prepared by treating a solution of 4-amino-5-(p-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine in CH<sub>2</sub>Cl<sub>2</sub>-TEA

with the 4-(dimethylamino)butylamine and heating the resulting mixture at reflux for 1 hour. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (SiO<sub>2</sub>, EtOAc/hexanes). The product was treated with excess 2M HCl (aq) followed by lyophilization to give the product as the tetrahydrochloride salt: IR (KBr) 3439, 1567, 1356, 1196; MS m/z 519/521 (M+H)<sup>+</sup>.

#### Example 202

##### 4-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(p-bromophenyl)pyrido[2,3-d]pyrimidine

A sample of the compound from Example 190 above, 4-formylamino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)-pyrido[2,3-d]pyrimidine (0.27 g, 0.6 mmol) in 3 mL of a 4:1 mixture of THF and DMF at 0°C was treated with NaH (60% dispersion, 36 mg, 0.9 mmol) and the solution was stirred for 0.5 hour. Allyl bromide (0.29 g, 2.4 mmol) was added, and the reaction mixture was stirred for an additional 0.5 hour. Aqueous workup followed by flash chromatography provided the title compound: LRMS m/z 488/490. IR (cm<sup>-1</sup>) 3428, 2910, 1696, 1551, 1362, 1193.

#### Example 203

##### 4-diacetylamino-5-(4-dimethylaminophenyl)-7-(p-bromophenyl)-pyrido[2,3-d]pyrimidine

This compound was isolated as a minor product from the reaction mixture of Example 190 above: LRMS m/z 504/506. IR (cm<sup>-1</sup>) 2922, 1726, 1550, 1360, 1197.

#### Example 204

##### 4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine

A solution of 5-aminopyridine-2-ethanone (1.15 g, 8.45 mmol), 3-bromobenzaldehyde (1.70 g, 9.2 mmol), malononitrile (0.61 g, 9.2 mmol), and

5 ammonium acetate (1.15 g, 15 mmol) in 25 mL of benzene was heated at reflux with  
azeotropic removal of water. After 6 hours the reaction mixture was concentrated.  
10 and the desired intermediate (1.82 g, 49%) was isolated following flash  
chromatography ( $\text{SiO}_2$ , EtOAc- $\text{CH}_2\text{Cl}_2$ ). LRMS m/z 366/368. The intermediate was  
5 suspended in 15 mL of formamide, and the reaction mixture was heated at 180 °C for  
4 hours. The solution was cooled to 25 °C, 10 mL of 4M HCl (aq) was added, and  
15 the mixture was stirred for 1 hour. The aqueous solution was neutralized with NaOH  
(aq), and the precipitate was collected by filtration. The title compound (1.3 g, 68%)  
was isolated following flash chromatography of the precipitate: LRMS m/z 393/395;  
10 IR (cm<sup>-1</sup>) 3481, 3161, 1620, 1573, 1483, 1359.

20 The 5-aminopyridine-2-carboxaldehyde starting material was prepared as follows:

204a. 5-amino-2-bromopyridine

25 A solution of 2-bromo-5-nitropyridine (5.1 g, 25 mmol) in 50 mL of a 10:1  
15 mixture of acetic acid and water was treated with iron powder (7.8 g, 140 mmol) in several  
portions over 20 minutes. After an additional 30 minutes the volatiles were removed  
under reduced pressure, and the residue was quenched with 5% aqueous sodium carbonate.  
30 The aqueous solution was extracted with methylene chloride, and the combined organic  
layer was dried (sodium sulfate) then concentrated in vacuo to provide the desired product  
20 as a white solid (4.25 g, 98%).

204b. 5-aminopyridine-2-ethanone

35 A sample of 5-amino-2-bromopyridine (4.25 g, 24 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.34 g, 2  
mole%), CuI (0.09 g, 2 mole%), and trimethylsilylacetylene (3.0 g, 31 mmol) were  
40 25 dissolved in 100 mL of a 4:1 mixture of triethylamine and acetonitrile, and the reaction  
mixture was stirred 24 hours at 25 °C. The reaction mixture was concentrated, and the  
residue was dissolved in 100 mL of a 10:1 mixture of acetone and water.  $\text{Hg}(\text{O}_2\text{CCF}_3)_2$   
45 (11.1 g, 26 mmol) and  $\text{H}_2\text{SO}_4$  (72 mmol) were added to the reaction mixture, and the  
solution was heated at reflux for 2 hours. The reaction mixture was cooled to 25 °C and  
30 neutralized with saturated aqueous sodium carbonate. The aqueous layer was extracted

with methylene chloride, then the combined organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. Flash chromatography ( $\text{SiO}_2$ , EtOAc-Hexanes) provided the title compound: LRMS  $m/z$  137 ( $M = H^+$ ); IR ( $\text{cm}^{-1}$ ) 3428, 1668, 1646, 1582, 1358, 1274.

#### Example 205

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyridyl)pyrido[2,3-d]pyrimidine trihydrochloride salt

Following the procedure of Example 204, 5-dimethylaminopyridine-2-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to give the title compound. The residue was triturated with excess HCl/ether, the volatiles were removed under reduced pressure, and the title compound was dried under high vacuum: LRMS  $m/z$  421/423. IR ( $\text{cm}^{-1}$ ) 3245, 1664, 1545, 1395.

The 5-dimethylaminopyridine-2-carboxaldehyde starting material was prepared as follows:

#### 205a. 3-N,N-dimethylaminopyridine

A solution of 3-aminopyridine (9.4 g, 0.10 mol) in a 1:1 mixture of formic acid (96%) and formaldehyde (37% aqueous solution) was heated at reflux for 18 hours. The volatiles were removed under reduced pressure and the residue was neutralized with saturated aqueous  $\text{NaHCO}_3$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , then the combined organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Flash chromatography ( $\text{SiO}_2$ , EtOAc-Hexanes) provided the title compound: (11.1 g, 91%), LRMS  $m/z$  123 ( $M + H^+$ ).

#### 205b. 2-bromo-5-N,N-dimethylaminopyridine

A solution of 3-N,N-dimethylaminopyridine (5.88 g, 48.1 mmol) in 150 mL of  $\text{CH}_2\text{Cl}_2$  at 0 °C was treated with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (20.7 g, 50 mmol) in several portions over 30 minutes. After 2 hours at 0 °C the reaction

5 mixture was concentrated, and the desired 2-bromo-5-N,N-dimethylaminopyridine was isolated following flash chromatography (16.5 g, 82%): LRMS m/z 201/203.

10 204c. 5-N,N-dimethylaminopyridine-2-ethanone

5 Following the procedure of Example 203b, 2-bromo-5-N,N-dimethylaminopyridine, except converting the compound to the trihydrochloride salt by treatment with HCl/ether, was converted to the title compound: LRMS m/z 165; IR (cm<sup>-1</sup>) 3480, 1666, 1581, 1368, 1272.

10 Example 206

20 4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyrazinyl)-pyrido[2,3-d]pyrimidine hydrochloride

25 Following the procedure of Example 204, 5-dimethylaminopyrazine-2-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to give the title compound. The residue was triturated with excess HCl/ether, the volatiles were removed under reduced pressure, and the title compound was dried under high vacuum: LRMS m/z 422/424. IR (cm<sup>-1</sup>) 3310, 1630, 1525, 1444, 1375.

20 The 5-dimethylaminopyrazine-2-carboxaldehyde starting material was prepared as follows:

35 206a. 5-dimethylaminopyrazine-2-ethanone

40 A solution of 5-hydroxypyrazine-2-carboxylic acid (4.0 g, 28.5 mmol) in 50 mL of thionyl chloride and 0.1 mL of DMF was heated at reflux for 8 hours. The volatiles were removed under reduced pressure, and the residue was dissolved in 20 mL of toluene. This solution was added to a solution of dimethyl malonate (4.75 g, 36 mmol), MgCl<sub>2</sub> (2.09 g, 22 mmol) and triethyl amine (7.08 g, 70 mmol) in 100 mL of toluene. The reaction mixture was stirred for 1 hour at 25 °C, quenched by addition of water, and the product was extracted with methylene chloride. The solvent was removed, the crude intermediate was dissolved in 25 mL of a 25:1

5 mixture of DMSO and water, and the resulting solution was warmed at 150 °C for 2  
hours. The reaction was quenched by addition of water, and the product was  
10 extracted with methylene chloride to provide 2-acetyl-5-chloropyrazine (LRMS m/z  
156). This intermediate was treated with aqueous dimethylamine at room  
5 temperature for 30 minutes to afford 5-dimethylaminopyrazine-2-ethanone (LRMS  
m/z 166): LRMS m/z 422/424: IR (cm<sup>-1</sup>) 3310, 1630, 1525, 1444, 1375.

#### Example 207

4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine

10 Following the procedure of Example 204, 2-oxobenzoxazolin-6-ethanone  
was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to  
prepare the title compound: LRMS m/z 434/436; IR (cm<sup>-1</sup>) 3095, 1760, 1579, 1481,  
25 1350.

15 The 2-oxobenzoxazolin-5-ethanone starting material was prepared as follows:

#### 207a. 2-oxobenzoxazolin-6-ethanone

30 DMF (9 mL) was added dropwise to AlCl<sub>3</sub> (58.7 g, 440 mmol) over 20  
minutes and the resulting suspension was stirred 15 minutes at 25 °C. Acetic  
20 anhydride (7.14 g, 70 mmol) and 2-benzoxazolinone (6.0 g, 44 mmol) were added  
35 and the reaction mixture was warmed at 80 °C and stirred for 4 hours. The mixture  
was cooled to 25 °C and poured into ice/H<sub>2</sub>O. The resulting precipitate was  
collected by filtration and dried under vacuum to provide the title compound (6.4 g,  
40 81%, LRMS m/z 177).

#### Example 208

45 4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)-  
pyrido[2,3-d]pyrimidine

Following the procedure of Example 204, 1-methyl-2-oxobenzoxazolin-5-ethanone was reacted with bromobenzaldehyde, malononitrile, and ammonium acetate to prepare the title compound: LRMS m/z 448/450; IR (cm<sup>-1</sup>) 3440, 1782, 1605, 1458, 1350.

The 1-methyl-2-oxobenzoxazolin-5-ethanone starting material was prepared as follows:

208a. 1-methyl-2-oxobenzoxazolin-5-ethanone

A solution of 2-oxobenzoxazolin-5-ethanone (from Example 206a, 2.50 g, 14.1 mmol) in 20 mL of a 4:1 mixture of THF and DMF at 0 °C was treated with NaH (60 % dispersion, 0.8 g, 20 mmol) and the mixture was stirred 20 minutes at 0 °C. Methyl iodide (3.97 g, 28 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 15 minutes. Saturated aqueous NaHCO<sub>3</sub> was added and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The desired product (2.55 g, 94%, LRMS m/z 191), was isolated following flash chromatography (SiO<sub>2</sub>, EtOAc-CH<sub>2</sub>Cl<sub>2</sub>).

Example 209

4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 173 by reaction with 3-methoxyphenylboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub> and aqueous sodium carbonate under Suzuki reaction conditions. IR (KBr) 3550-3250, 3240-2760, 1580, 1560, 1540, 1350; H. Rcs. MS m/z 496.1902 (M+H)<sup>+</sup>.

Example 210

4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 157, except substituting 1-(4-dimethylaminophenyl)-ethanone for the R<sup>1</sup> reagent and 2-(2-bromophenyl)-

acetaldehyde for the R<sup>3</sup> reagent of Example 157, the title compound was prepared as shown in Table 6.

Table 6

| Ex. No. | Name   | R <sup>1</sup> Reagent (for 7-position) | R <sup>3</sup> Reagent (for 5-position) | Analytical Data                               |
|---------|--|---|---|---|
| 210     | 4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine | 1-(4-dimethylaminophenyl)-ethanone      | 2-(2-bromophenyl)-acetaldehyde          | IR (KBr); MS m/z 434,436 (M+H) <sup>+</sup> . |

## Example 211

4-amino-5-(2-((thiophene-2-yl)phenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 173 by reaction with 2-thiopheneboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub> and aqueous sodium carbonate under Suzuki reaction conditions. IR (KBr) 3640-3240, 3240-2800, 1580, 1560, 1540, 1350; H. Res. MS m/z 466.2070 (M+H)<sup>+</sup>.

## Example 212

4-amino-5-(2-((thiophene-3-yl)phenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 173 by reaction with 3-thiopheneboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub> and aqueous sodium carbonate under Suzuki reaction conditions. IR (KBr) 3640-3240, 3240-2800, 1580, 1560, 1540, 1350; H. Res. MS m/z 466.2057 (M+H)<sup>+</sup>.



Examples 213-222

Following the procedures of Example 1, except substituting the appropriate reagents for R<sup>4</sup> and R<sup>1</sup> as indicated in Table 7 below. compounds of Examples 212-222 were prepared.

Table 7Examples 213-222

| Ex. No. | Name   | R <sup>4</sup> Reagent (for 7-position)                         | R <sup>1</sup> Reagent (for 5-position) | Analytical Data   |
|---------|--|---|---|---|
| 213     | 4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;         | 1-(4-(N-formyl-N-(2-methoxy)ethylamino)phenyl)-ethanone         | 3-bromo-benzaldehyde                    | IR (KBr) 3490, 1689, 1120, 800 cm <sup>-1</sup> ; MS m/z 478/480 (M+H) <sup>+</sup> . |
| 214     | 4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;                  | * 1-(4-(N-2-methoxyethyl)amino)phenyl-ethanone                  | 3-bromo-benzaldehyde                    | IR (KBr) 3330, 2925, 1675, 800 cm <sup>-1</sup> ; MS m/z 451/453 (M+H) <sup>+</sup> . |
| 215     | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine; | 1-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)-ethanone | 3-bromo-benzaldehyde                    | IR (KBr) 3440, 1600, 1160, 810 cm <sup>-1</sup> ; MS m/z 477/479 (M+H) <sup>+</sup> . |

|     |  |   |                      |  |
|-----|--|---|----------------------|--|
| 216 | 4-amino-5-(3-bromophenyl)-7-(4-(2-methoxy)acetylaminophenyl)pyrido[2,3-d]pyrimidine;           | ** 1-(4-(2-methoxyacetylaminophenyl)-ethanone           | 3-bromo-benzaldehyde | IR (KBr) 3480, 1520, 710 cm <sup>-1</sup> ; MS m/z 464, 466 (M+H) <sup>+</sup> .                     |
| 217 | 4-amino-5-(3-bromophenyl)-7-(4-(4-formylamino)phenyl)pyrido[2,3-d]pyrimidine;                  | *** 1-(4-(formylamino)phenyl)-ethanone                  | 3-bromo-benzaldehyde | IR (KBr) 3475, 1690, 1355, 800 cm <sup>-1</sup> ; MS m/z 420/422 (M+H) <sup>+</sup> .                |
| 218 | 4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)acetylaminophenyl)pyrido[2,3-d]pyrimidine;    | **** 1-(4-(2-(dimethylamino)acetylaminophenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3452, 1605, 1250, 590 cm <sup>-1</sup> ; MS m/z 477/479 (M+H) <sup>+</sup> .                |
| 219 | 4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine;           | 1-(4-(2-oxo-3-oxazolidinyl)phenyl)-ethanone             | 3-bromo-benzaldehyde | IR (KBr) 3480, 1750, 1400, 700 cm <sup>-1</sup> ; MS m/z 462/464 (M+H) <sup>+</sup> .                |
| 220 | 4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride | 1-(6-(2-propyl)-3-pyridinyl)-ethanone                   | 3-bromo-benzaldehyde | IR (KBr) 3474, 3098, 1636, 1566, 1499, 1352, 1282 cm <sup>-1</sup> ; MS m/z 393 (M+H) <sup>+</sup> . |

|     |  |  |                      |  |
|-----|--|--|----------------------|--|
| 221 | 4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine dihydrochloride | 1-(3-methyl-4-pyrrolidinylphenyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3440, 1640, 1607, 1586, 1370 cm <sup>-1</sup> ; MS m/z 433 (M+H) <sup>+</sup> . |
| 222 | 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride     | 1-(6-imidazolyl-3-pyridinyl)-ethanone      | 3-bromo-benzaldehyde | IR (KBr) 3028, 1641, 1607, 1595, 1375 cm <sup>-1</sup> ; MS m/z 417 (M+H) <sup>+</sup> . |

\*prepared by deformylation of Example 213 with dilute HCl in methanol.

\*\*prepared by acylation of Example 213 with 2-methoxyacetyl chloride/pyridine.

\*\*\*prepared by formylation of the 7-(3-bromophenyl)-2-cyano-5-(4-aminophenyl)pyridine-2-amine intermediate.

\*\*\*\*prepared by acylation of Example 213 with the 2-(dimethylamino)acetyl chloride.

#### Examples 223-225

Following the procedures of Example 157, except substituting the appropriate reagents for the R<sup>1</sup> and R<sup>3</sup> reagents of Example 157 as indicated in Table 8 below, compounds of Examples 223-225 were prepared.

Table 8

#### Examples 223-225

| Ex. No. | Name | R <sup>1</sup> Reagent (for 7-position) | R <sup>3</sup> Reagent (for 5-position) | Analytical Data |
|---------|------|---|---|-----------------|
|---------|------|---|---|-----------------|

|     |   |                                    |  |   |
|-----|---|------------------------------------|--|---|
| 223 | 4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine                      | 1-(4-diethylaminophenyl)-ethanone  | 2-phenyl-acetaldehyde                                      | IR (KBr) 3450,3380,2850-3200,1605,1580,1560,1540; H. Res. MS m/z 384.2176 (M+H) <sup>+</sup> .      |
| 224 | 4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine | 1-(4-diethylaminophenyl)-ethanone  | * from Example 170, palladium coupling with 3-aminopropyne | IR (KBr) 2400-3450,2050,2120,1650,1605,1540; MS m/z 437 (M+H) <sup>+</sup> .                        |
| 225 | 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine         | 1-(4-dimethylaminophenyl)-ethanone | 2-(2-bromophenyl)-propionaldehyde                          | IR (KBr) 3520,3250-3500,2850-3150,1605,1580,1560,1540; H. Res. MS m/z 448.1137 (M+H) <sup>+</sup> . |

\*prepared from the compound of Example 170 by reaction with propargylamine, CuI and Pd(PPh<sub>3</sub>)<sub>4</sub> under Suzuki reaction conditions.

#### Examples 226-228

Following the procedures of Example 1, except substituting the appropriate reagents for R<sup>4</sup> and R<sup>5</sup> as indicated in Table 9 below, compounds of Examples 226-228 were prepared.

Table 9

Examples 226-228

| Ex. No. | Name   | R <sup>1</sup> Reagent (for 7-position)      | R <sup>2</sup> Reagent (for 5-position) | Analytical Data  |
|---------|--|--|---|--|
| 226     | 4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine         | 1-(4-bromophenyl)-ethanone                   | 3-bromo-benzaldehyde                    | IR (KBr) 3456, 3053, 16600, 1556 cm <sup>-1</sup> ; MS m/z 420 (M+H) <sup>+</sup>                        |
| 227     | 4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)-pyrido[2,3-d]pyrimidine          | 1-(4-(N-morpholinyl)phenyl)ethanone          | furan-2-carboxaldehyde                  | IR (KBr) 3460, 1600, 1580, 1457 cm <sup>-1</sup> ; MS m/z 374 (M+H) <sup>+</sup>                         |
| 228     | 4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine | 1-(5-(2-(dimethylamino)pyrimidinyl))ethanone | 3-bromo-benzaldehyde                    | IR (KBr) 3442, 1640, 1604, 1577, 1536, 1408, 1367, 1348 cm <sup>-1</sup> ; MS m/z 422 (M+H) <sup>+</sup> |

## Example 229

4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine

A solution of 4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine (Example 71, 310 mg, 0.79 mmol) in 2 mL of acetic acid was treated with sodium cyanate (56 mg, 0.87 mmol), and the reaction mixture was stirred for 30 minutes at 25 °C. The solution was concentrated and the residue was suspended in aqueous

NaHCO<sub>3</sub>. The crude product was collected by filtration, then purified by flash chromatography. The product was dissolved in methanol and treated with excess 2M aqueous HCl to provide the hydrochloride salt: LRMS m/z 435/437. IR (cm<sup>-1</sup>) 3442, 2212, 3186, 3059, 1681, 1582, 1525, 1358.

#### Example 230

#### 4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 157, except substituting 1-(4-diethylamino-phenyl)-ethanone for the R<sup>4</sup> reagent and 1-phenylmethylpiperidine-3-carboxaldehyde (prepared as described by Gilligan et al., J. Med. Chem., 35:4344-4361 (1992)) for the R<sup>3</sup> reagent thereof, the title compound was prepared. The treatment with aqueous HCl was omitted, and the free base was obtained. IR (KBr) 3440, 3100-2800-1640, 1605, 1595, 1535 cm<sup>-1</sup>; MS m/z 467 (M+H)<sup>+</sup>; mp 218-220 °C.

#### Examples 231-243

Following the procedures of Example 1, except substituting the appropriate reagents for R<sup>4</sup> and R<sup>3</sup> as indicated in Table 10 below, compounds of Examples 230-243 were prepared. In some cases, the treatment with aqueous HCl was omitted, and the free bases were obtained. Some compounds were isolated as the TFA salt following purification via high pressure liquid chromatography (HPLC).

Table 10

Examples 231-243

| Ex. No. | Name  | R <sup>1</sup> Reagent (for 7-position)            | R <sup>1</sup> Reagent (for 5-position) | Analytical Data  |
|---------|---|--|---|--|
| 231     | 4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-pyridinylpyrido[2,3-d]pyrimidine; | 1-(6-(3-methyl-5-isoxazolyl))-3-pyridinyl-ethanone | 3-bromo-benzaldehyde                    | IR (KBr) 3484, 1635, 1574, 1562, 1352 cm <sup>-1</sup> ; MS m/z 459 (M+H) <sup>+</sup> .             |
| 232     | 4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine;                  | 1-(6-chloro-3-pyridinyl)-ethanone                  | 3-bromo-benzaldehyde                    | IR (KBr) 3478, 1608, 1574, 1542 cm <sup>-1</sup> ; MS m/z 414 (M+H) <sup>+</sup> .                   |
| 233     | 4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine;                 | 1-(6-methoxy-3-pyridinyl)-ethanone                 | 3-bromo-benzaldehyde                    | IR (KBr) 3484, 1635, 1560, 1348 cm <sup>-1</sup> ; MS m/z 409 (M+H) <sup>+</sup> .                   |
| 234     | 4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl))-3-pyridinylpyrido[2,3-d]pyrimidine;    | 1-(6-(1,2,4-triazol-4-yl))-3-pyridinyl-ethanone    | 3-bromo-benzaldehyde                    | IR (KBr) 3494, 1612, 1579, 1467, 1359, 1271, 1233 cm <sup>-1</sup> ; MS m/z 445 (M+H) <sup>+</sup> . |

|     |  |  |                           |   |
|-----|--|--|---------------------------|---|
| 235 | 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;                | 1-(2-morpholinyl-5-pyrimidinyl)-ethanone               | 3-bromo-benzaldehyde      | IR (KBr) 3434, 1637, 1608, 1585, 1335, $\text{cm}^{-1}$ ; MS $m/z$ 463 (M+H) <sup>+</sup> . |
| 236 | 4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine;                        | 1-(4-pyrrolidinylphenyl)-ethanone                      | 2-thiazole-carboxaldehyde | IR (KBr) 3400, 1637, 1608, 1532, $\text{cm}^{-1}$ ; MS $m/z$ 376 (M+H) <sup>+</sup> .       |
| 237 | 4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-d]pyrimidine;                   | 1-(6-pyrazolyl-3-pyridinyl)-ethanone                   | 3-bromo-benzaldehyde      | IR (KBr) 3474, 1580, 1562, 1492, 1395, $\text{cm}^{-1}$ ; MS $m/z$ 444 (M+H) <sup>+</sup> . |
| 238 | 4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)-pyrido[2,3-d]pyrimidine;                 | 1-(4-(1-methyl-ureido)phenyl)-ethanone                 | 3-bromo-benzaldehyde      | IR (KBr) 3400, 1665, 1350 $\text{cm}^{-1}$ ; MS $m/z$ 450 (M+H) <sup>+</sup> .              |
| 239 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-pyrido[2,3-d]pyrimidine; | 1-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-ethanone | 3-bromo-benzaldehyde      | IR (KBr) 3475, 1578, 1553, 1482, 1396, $\text{cm}^{-1}$ ; MS $m/z$ 484 (M+H) <sup>+</sup> . |



|     |   |   |                      |   |
|-----|---|---|----------------------|---|
| 240 | 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine;<br>*       | 1-(3-fluoro-4-(N-methylamino)phenyl)-ethanone               | 3-bromo-benzaldehyde | IR (KBr) 3448, 1600, 1525, 1476, cm <sup>-1</sup> ; MS m/z 484 (M+H) <sup>+</sup> . |
| 241 | 4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine;<br>* | 1-(3-fluoro-4-(N-methylamino)phenyl)-ethanone               | 3-bromo-benzaldehyde | IR (KBr) 3465, 1607, 1546, 1350, cm <sup>-1</sup> ; MS m/z 481 (M+H) <sup>+</sup> . |
| 242 | 4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)-phenyl)pyrido[2,3-d]pyrimidine;             | 1-(4-(N-methyl-N-methylsulfonylamino)phenyl)-ethanone       | 3-bromo-benzaldehyde | IR (KBr) 3470, 1650, 1570, 1338, cm <sup>-1</sup> ; MS m/z 484 (M+H) <sup>+</sup> . |
| 243 | 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;        | 1-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)-ethanone | 3-bromo-benzaldehyde | IR (KBr) 3460, 1680, 1580, 1330 cm <sup>-1</sup> ; MS m/z 485 (M+H) <sup>+</sup> .  |

\* separated by chromatography from the same reaction mixture; formylation occurs during the cyclization step

5

Example 2444-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine  
dihydrochloride

10

5 A sample of 4-(3-bromophenyl)-3-cyano-6-(1-methyl-5-indolyl)pyridine-2-amine was heated at reflux in formamide. The reaction was monitored by TLC, and  
15 when the reaction was complete the mixture was cooled to room temperature. The product was allowed to precipitate, then recovered by filtration and washed with water. Additional product was extracted from the filtrate. The product was purified  
20 by column chromatography eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> and converted to the hydrochloride salt by treatment with ether/HCl. The salt was isolated and dried under vacuum to give the title compound. LRMS m/z 432/434; IR (cm<sup>-1</sup>) 3500, 3400, 3300, 3200-2800, 1610, 1580, 1560, 1540.

25

The 4-(3-bromophenyl)-3-cyano-6-(1-methyl-5-indolyl)pyridine-2-amine  
15 starting material was prepared as follows:

30

244a. 5-bromo-1-methylindoline

Acetic acid (60 mL) was added to a mixture of 5-bromo-1-methylindole (10 g, 47.6 mmol) and sodium cyanoborohydride (8 g). After one hour at 15 °C, the  
20 reaction was basified with aqueous NaOH and extracted with toluene. The organic phase was dried over MgSO<sub>4</sub> and concentrated to a powder under vacuum. This material was purified by flash chromatography to give the title compound, 8.62 g (82 %): MS 212, 214 [M+H]<sup>+</sup>.

35

40

244b. 5-acetyl-1-methylindoline

A mixture of 5-bromo-1-methylindoline (8.6 g, 40.7 mmol), trimethylsilylacetylene (12 mL), palladium bis-triphenylphosphine dichloride (600 mg), CuI (620 mg) and triethylamine (16 mL) in acetonitrile (20 mL) was heated at  
45 75 °C for 3 days, then cooled and concentrated in vacuo. The residue was dissolved in 120 mL of 1:1 ethyl acetate/hexane, and the solids were removed by filtration.

50

55

5 The solvent was removed and a sample of the residue (5 g) was dissolved in 90% aqueous acetone (44 mL). To this solution was added sulfuric acid (2.2 g), and  
10  $\text{Hg}(\text{OCOCF}_3)_2$  (9 g). The reaction was heated at reflux for 20 minutes, cooled, made basic with aqueous sodium hydroxide and extracted with ethyl acetate. The organic  
5 layer was dried over  $\text{MgSO}_4$  and concentrated to an oil, which was purified by flash chromatography to give 850 mg of the title compound: MS 176  $[\text{M}+\text{H}]^+$ .

15 244c. 4-(3-bromophenyl)-3-cyano-6-(1-methyl-5-indolyl)pyridine-2-amine

Prepared by condensation of 1',1'-dicyano-3-bromostyrene (prepared by  
10 condensation of 3-bromobenzaldehyde with malononitrile in ethanol in the presence of a catalytic amount of glycine) and the 5-acetyl-1-methylindoline (the  $\text{R}^1$  reagent)  
20 with ammonium acetate in ethanol. After 3.5 hours, the mixture was cooled, and the solvent was removed. The residue was purified by flash chromatography, eluting  
25 with methylene chloride, to give the title compound (588 mg, 30% yield; MS  $m/z$  394  $(\text{M}+\text{H})^+$ ).

30 Example 245

20 4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-d]pyrimidine  
tetrahydrochloride

35 The title compound was prepared according to the procedure of Example 1, except substituting 1-methyl-5-acetyl-benzimidazole (prepared according to the procedure of D. J. Evans et. al., J. Chem. Soc. Perkin Trans. II, 1978, 865) for the 4-  
40 dimethylaminobenzaldehyde (the  $\text{R}^1$  reagent) therein. IR (KBr) 3650-3230, 3230-2000,  
25 1635, 1605, 1590, 1555, 1365  $\text{cm}^{-1}$ ; MS  $m/z$  431/433, 431.0605  $(\text{M}+\text{H})^+$ .

45 Example 246

30 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine  
tetrahydrochloride

5

246a. 6-(1-butoxyethenyl)-3-chloropyridazine

10

To a solution of 20 g (200 mmol) of butyl vinyl ether in 80 mL of THF at -78 °C was added 130 mL of a 1.7 M solution of t-butyl lithium in pentane over about 20 minutes. The yellow suspension was stirred while allowing to warm to 0 °C. THF (150 mL) was added, and the mixture cooled to -78 °C and a solution of 23 mL (200 mmol) of trimethyl borate in 50 mL of THF was added. The reaction was warmed to 20 °C, 20 mL of methanol was added, and the solution concentrated in vacuo. The residue was diluted with 400 mL of dioxane, and 20.9 g (140 mmol) of 3,6-dichloropyridazine, 2.31 g of Pd(PPh<sub>3</sub>)<sub>4</sub>, and 200 mL of 2 M- aqueous sodium carbonate was added. The reaction was heated to reflux over one hour, then cooled and filtered to remove solids. The filtrate was concentrated in vacuo and partitioned between ethyl acetate and 1 M sodium hydroxide. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and purified by flash chromatography to give 6.3 g (21%) of the title compound. MS {M + }+ 213, 215.

15

20

25

15

246b. 1-(6-chloropyridazin-3-yl)ethanone

30

A mixture 6.3 g of the compound from Step 246a in 40 mL of dimethoxyethane, 10 mL of water, and 4 mL of 12 M HCl was stirred for 20 minutes, then 125 mL of water was added, and the reaction was neutralized with 12 g of NaHCO<sub>3</sub>. The reaction was extracted with ethyl acetate, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give a yellow solid. 4.7 g.

35

246c. 1-(3-(6-(dimethylamino)pyridazin-3-yl))ethanone (the R<sup>1</sup> reagent)

40

25

A solution of 1.57 g (10 mmol) of 1-(6-chloropyridazin-3-yl)ethanone (from Step 246b) in 15 mL of dimethoxyethane was treated with 50 mmol of 40% aqueous dimethylamine. After one hour, the reaction was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water. The organic phase was dried over CH<sub>2</sub>Cl<sub>2</sub>, and concentrated in vacuo to give the title compound.

45

50

55

246d. 3-acetyl-6-(dimethylamino)pyridazine

The title compound was prepared by condensing 1,1-dicyano-(3-(3-bromophenyl)propene (the R<sup>1</sup> reagent) with the compound from Step 246c (the R<sup>1</sup> reagent) and ammonium acetate in ethanol according to the procedure of Example 157d.

246e. 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine tetrahydrochloride

The title compound was prepared from the compound of Step 246d according to the procedure of Example 157, except substituting formamide for the ammonium sulfate and triethyl orthoformate thereof.

Examples 247-248

Following the procedures of Example 246, except in step (c) substituting the appropriate reagents for methylamine as indicated in the Table 11A below, compounds of Examples 247-248 were prepared.

Table 11AExamples 247-248

| Ex. No. | Name   | reagent of step c | Analytical Data   |
|---------|--|-------------------|---|
| 247     | 4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine dihydrochloride | morpholine        | IR (KBr) 3600-3200, 3000, 1630, 1605, 1590, 1550 cm <sup>-1</sup> ; MS m/z 464/466, 464.0829 (M+H) <sup>+</sup> ; |

|     |   |             |  |
|-----|---|-------------|--|
| 248 | 4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine dihydrochloride | pyrrolidine | IR (KBr) 3600-3250, 3100-2800, 1640, 1605, 1560 $\text{cm}^{-1}$ ; MS $m/z$ 448/450, $(M+H)^+$ ; |
|-----|---|-------------|--|

#### Examples 249-251

Following the procedures of Example 244, except in step (c) first substituting the appropriate reagent for  $R^4$  as indicated in Table 11B below for the  $R^4$  reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds of Examples 249-251 were prepared. In some cases, the hydrochloride salts were not prepared.

Table 11B

#### Examples 249-260

| Ex. No. | Name   | $R^4$ Reagent (for 7-position)  | Analytical Data  |
|---------|--|---------------------------------|--|
| 249     | 4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-d]pyrimidine dihydrochloride | 2-acetyl-5-morpholinyl-pyrazine | IR (KBr) 3478, 3058, 1562, 1542, 1378, 1306 $\text{cm}^{-1}$ ; MS $m/z$ 464/466, $(M+H)^+$ ; |

|     |   |  |   |
|-----|---|--|---|
| 250 | 4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-pyrazinyl)pyrido[2,3-d]pyrimidine dihydrochloride | 2-acetyl-5-(N-(2-methoxyethyl)-N-methylamino)-pyrazine | IR (KBr) 3482, 3299, 3053, 1612, 1540, 1310 cm <sup>-1</sup> ; MS m/z 466/468, (M+H) <sup>+</sup> ; |
| 251 | 4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-d]pyrimidine hydrochloride                       | 1-((4-acetylphenyl)-methyl)-morpholine                 | IR (KBr) 3040, 1680, 1640, 1605, 1580, 1400 cm <sup>-1</sup> ; MS m/z 466/468, (M+H) <sup>+</sup> ; |

Example 252

4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride

Step 252a. 1-(5-bromo-2-pyridyl)ethanone, ethylene ketal

A solution of dibromopyridine (5.2 g, 21.95 mmol), tributyl(1-ethoxyvinyl)tin (9.11 g, 25.24 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.7 g, 0.8 mmol), and (2-furyl)<sub>3</sub>P (0.37 g, 1.6 mmol) in 50 mL of toluene/THF (5:1) was warmed at reflux for 10 hours. The reaction mixture was concentrated, and the crude product was purified by elution through a short column of silica gel. The resulting enol-ether compound, ethylene glycol (2.79 g, 45 mmol), and p-toluene sulfonic acid (0.1 g) were dissolved in 50 mL of toluene and the solution was warmed at reflux for 10 hours. The reaction mixture was quenched by the addition of saturated aqueous NaHCO<sub>3</sub>, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated under reduced pressure, and the resulting crude product was purified by flash chromatography to provide the title compound (3.68 g, 79%).

Step 252b. 1-(5-(bis(2-methoxyethyl)amino)-2-pyridyl)ethanone

Following literature procedure (J. Org. Chem. 1996, 61, 720), a suspension of the compound from step 252a, bis(2-methoxyethyl)amine, t-BuONa, Pd<sub>2</sub>(dba)<sub>3</sub>, and BINAP toluene was warmed at 80 °C for 8 hours. The reaction mixture was quenched by the addition of saturated aqueous NaHCO<sub>3</sub> and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was concentrated and the resulting residue was dissolved in 20 mL THF/3 M HCl (4:1) and stirred for 4 h. The reaction mixture was neutralized by the addition of 2 M NaOH (aq) and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was dried, concentrated under reduced pressure, and the crude product was purified by flash chromatography to provide the title compound

Step 252c. 4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride

Following the procedures of Example 244, except in step (c) first substituting the reagent from Step 252b for the R<sup>4</sup> reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the free base of the title compound was prepared. The title compound was prepared from this by treatment with HCL in ether. IR (KBr) 3440, 1635, 1605, 1580, 1360 cm<sup>-1</sup>; MS m/z 466/468, (M+H)<sup>+</sup>.

Examples 253-260

Following the procedures of Example 244, except in step (c) first substituting the appropriate reagent for R<sup>4</sup> as indicated in Table 11B below for the R<sup>4</sup> reagent of Example 244 step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds of Examples 253-260 were prepared. In some cases, the hydrochloride salts were not prepared.



| Ex. No. | Name   | R <sup>1</sup> Reagent (for 7-position)           | Analytical Data   |
|---------|--|---|---|
| 253     | 4-amino-5-(3-bromophenyl)-7-(4-(imidazolymethyl)-phenyl)pyrido[2,3-d]pyrimidine trihydrochloride             | 1-((4-acetylphenyl)-methyl)imidazole              | IR (KBr) 3105, 1645, 1620, 1570, 1350 cm <sup>-1</sup> ; MS m/z 466/468, (M+H) <sup>+</sup> ;       |
| 254     | 4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine trihydrochloride          | 1-(5-morpholinyl-2-pyridyl)ethanone *             | IR (KBr) 3297, 3081, 1646, 1564, 1494, 1362 cm <sup>-1</sup> ; MS m/z 463/465, (M+H) <sup>+</sup> ; |
| 255     | 4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-d]pyrimidine dihydrochloride        | 1-(4-((dimethylamino)methyl)phenyl)-ethanone      | IR (KBr) 3308, 1645, 1590, 1560, 1375 cm <sup>-1</sup> ; MS m/z 509/511, (M+H) <sup>+</sup> ;       |
| 256     | 4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine dihydrochloride | 1-(5-(4-hydroxypiperidinyl)-2-pyridyl)ethanone ** | IR (KBr) 3000, 1650, 1600, 1580, 1550, 1400 cm <sup>-1</sup> ; MS m/z 477/479, (M+H) <sup>+</sup> ; |

|     |   |  |   |
|-----|---|--|---|
| 257 | 4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine dihydrochloride | 5-acetyl-2-pyridinemethanamine               | IR (KBr) 3477, 3060, 1678, 1638, 1566, 1495, 1319 cm <sup>-1</sup> ; MS m/z 435/437, (M+H) <sup>+</sup> ; |
| 258 | 4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine                             | 2-acetyl-5-(2-propenyl)-pyridine             | IR (KBr) 3085, 1562, 1485, 1357 cm <sup>-1</sup> ; MS m/z 418/420, (M+H) <sup>+</sup> ;                   |
| 259 | 4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine hydrochloride  | 6-acetyl-3-(2-methoxyethyl)-benzoxazol-2-one | IR (KBr) 3440, 1770, 1625, 1605, 1580, 1360 cm <sup>-1</sup> ; MS m/z 492/494, (M+H) <sup>+</sup> ;       |
| 260 | 4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine                      | N-(1-(4-acetylphenyl)ethyl)-formamide        | IR (KBr) 3283, 3054, 1678, 1631, 1547, 1352 cm <sup>-1</sup> ; MS m/z 448/450, (M+H) <sup>+</sup> ;       |

\* Prepared as in Ex. 252b, except substituting morpholine for the bis(2-methoxyethyl)amine thereof.

\*\* Prepared as in Ex. 252b, except substituting 4-hydroxypiperidine for the bis(2-methoxyethyl)amine thereof.

Example 2614-amino-5-(3-pyridyl)-7-(4-dimethylamino)phenylpyrido[2,3-d]pyrimidine

The compound was prepared by using the method generally described above in Scheme 3 and the associated examples using 1-(4-dimethylaminophenyl)ethanone as the R<sup>4</sup> reagent (7-position) and nicotinaldehyde as the R<sup>3</sup> reagent (5-position). IR (cm<sup>-1</sup>) 3305.8, 2922, 1606, 1578, 1535, 1360. MS (M+H) 342.

Example 2624-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride

The title compound was prepared by using the method described in Example 200, except substituting methylamine for the 2-(dimethylamino)ethylamine thereof. MS (M+H), 478 (1Br); IR (cm<sup>-1</sup>) 3455, 3047, 2959, 1580, 1351, 1234.

Example 2634-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride

The title compound was prepared by using the method described in Example 200, except substituting 2-methoxyethylamine for the 2-(dimethylamino)ethylamine thereof. MS (M+H), 522 (1Br); IR (cm<sup>-1</sup>) 3415, 2920, 1569, 1321, 1234.

Example 2644-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochlorideStep 264a. 1-(4-(1-Methylimidazol-2-yl)phenyl)ethanone

A solution of N-methyl imidazole (0.90 g, 11.0 mmol) in 12 mL of THF at -78 °C was treated with n-BuLi (7.5 mL, 1.6 M solution in hexanes, 12.0 mmol) for 0.5 hours at -78 °C. Next, ZnCl<sub>2</sub> (20 mL, 1.0 M solution in Et<sub>2</sub>O, 20 mmol) was added, and the solution was warmed to 25°C. To this solution was added Pd(PPh<sub>3</sub>)<sub>4</sub> (70 mg, 0.06 mmol)

5 followed by 4-iodoacetophenone ethylene acetal (prepared from iodoacetophenone and  
ethylene glycol in the presence of an acid catalyst by standard procedures), and the  
10 reaction mixture was heated at reflux for 4 hours. The solution was then cooled to 25 °C  
and quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (10 mL). The aqueous layer  
5 was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layer was concentrated under  
reduced pressure. The residue was dissolved in 30 mL of THF, 15 mL of 3 M aqueous  
15 HCl was added, and the mixture was stirred for 2 hours at 25 °C. The solution was  
neutralized by the addition of saturated aqueous NaHCO<sub>3</sub>, and the aqueous layer was  
extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was dried (MgSO<sub>4</sub>) then  
20 concentrated under reduced pressure. The crude product was purified by flash  
chromatography to provide the title compound (0.89 g, 64%).

25 Step 264b. 4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-  
d]pyrimidine trihydrochloride

15 Following the procedures of Example 244, except in step (c) first substituting the  
R<sup>4</sup> reagent from Step 264a for the R<sup>4</sup> reagent of Example 244 step c, and secondly  
30 performing the condensation with ammonium acetate substituting dichloroethane as the  
solvent in place of the ethanol solvent in Example 244 step c, the title compound was  
prepared. MS (M+H) 458 (1Br); IR (cm<sup>-1</sup>) 3051, 2948, 1577, 1474, 1354.

35 Examples 265-267

Following the procedures of Example 244, except in step (c) first substituting the  
appropriate reagent for R<sup>4</sup> as indicated in the Table below for the R<sup>4</sup> reagent of Example  
40 244 step c, and secondly performing the condensation with ammonium acetate substituting  
25 dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the  
compounds of Examples 264-285 were prepared. In Ex. 266, the hydrochloride salt was  
not prepared.

| Ex. No. | Name   | R <sup>1</sup> Reagent (for 7-position)     | Analytical Data   |
|---------|--|---|---|
| 265     | 4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine           | 1-(4-(aminomethyl)phenyl)ethanone           | MS (M+H), 460; IR (cm <sup>-1</sup> ) 3024, 2933, 1550, 1493, 1328                          |
| 266     | 4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine | 1-(2-bromo-4-(dimethylamino)phenyl)ethanone | MS (M+H), 500 (2 Br); IR (cm <sup>-1</sup> ) 3049, 2949, 1536, 1468, 1320                   |
| 267     | 4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine    | 1-(4-(dimethylaminoethyl)phenyl)ethanone    | MS (M+H), 448 (1 Br); IR (cm <sup>-1</sup> ) 3420, 3000, 2980, 1635, 1610, 1590, 1435, 1415 |

Example 2684-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine

A suspension of the compound of Example 63 (0.80 g, 1.59 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, and 3-dimethylaminoprop-1-yne in 20 mL of DMF/TEA (4:1) was heated at 50 °C for 3 hours. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography to provide the title compound (0.50 g, 68 %). MS (M+H), 459 (1Br); IR (cm<sup>-1</sup>) 3027, 2964, 1513, 1470, 1360.

Examples 269-271

Following the procedures of Example 268, except substituting the reagent compound shown in the table below for the 3-dimethylaminoprop-1-yne of Example 268, the compounds shown in the table below were prepared.

| Ex. No. | Name   | Reagent                      | Analytical Data  |
|---------|--|------------------------------|--|
| 269     | 4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine | 1,1-dimethyl-propargyl amine | MS (M+H), 459 (1Br); IR (cm <sup>-1</sup> ) 3041, 2967, 1562, 1484, 1319 |
| 270     | 4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine       | dimethyl phosphite           | MS (M+H), 486 (1Br); IR (cm <sup>-1</sup> ) 3105, 2912, 1625, 1437, 1350 |
| 271     | 4-amino-5-(3-bromophenyl)-7-(4-(3-(methoxypropynyl)pyrido[2,3-d]pyrimidine             | methyl propargyl ether       | MS (M+H), 446 (1Br); IR (cm <sup>-1</sup> ) 3053, 2929, 1560, 1484, 1352 |

Example 2724-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine

A solution of 4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine (the compound of Example 37, (0.47 g, 1.17 mmol) in 15 mL of 6 M HCl (aqueous) was heated at 60 °C for 8 hours. The mixture was lyophilized and the crude product was purified by flash chromatography to provide the title compound (0.14 g, 28%). MS (M+H), 422 (1Br); IR (cm<sup>-1</sup>) 3064, 2628, 1692, 1403, 1273.

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Example 273

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4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-pyrido[3,2-b]-1,4-oxazinyl)pyrido[2,3-d]pyrimidine

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Step 273a. 7-acetyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one

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A solution of 2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (9.8 g, 65.27 mmol, Aldrich) in 120 mL of THF/MeOH (5:1) was treated with 0.4 mL of concentrated HCl (aqueous) followed by N-bromosuccinimide (17.8 g, 100 mmol) in several portions over 10 minutes. After 12 hours at 25 °C the reaction mixture was quenched by the addition of saturated aqueous NaHSO<sub>3</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated under reduced pressure, and purified by flash chromatography to provide 7-bromo-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (8.4 g, 56%). A mixture of 7-bromo-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (3.2 g, 14 mmol), tributyl(1-ethoxyvinyl)tin (6.1 g, 17 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.5 g, 0.56 mmol), and (2-furyl)<sub>3</sub>P (0.3 g, 1.2 mmol) in 30 mL of toluene/THF (5:1) was warmed at reflux for 10 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 50 mL of THF. 15 mL of 4 M HCl (aqueous) was added, and the mixture was stirred for 4 hours at 25 °C. The solution was neutralized by the addition of NaHCO<sub>3</sub> (aqueous), and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and the crude product was purified by flash chromatography to provide 7-acetyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (2.37 g, 88%). MS (M+H), 463 (1 Br); IR (cm<sup>-1</sup>) 3400, 3200-2800, 1700, 1640, 1605, 1590, 1395, 1380, 1345.

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Step 273b. 7-acetyl-4-methyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one

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The compound from step 273 a was treated with methyl iodide and NaH in 1:1 THF/DMF for 6 hours at 0 °C to 25 °C. The reaction was quenched with aqueous sodium

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bicarbonate solution, the mixture was extracted with dichloromethane, and the residue was purified by chromatography to give the title compound. MS (M+H), 407.

Step 273c. 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazinyl)pyrido[2,3-d]pyrimidine

Following the procedure of Example 244 Step c, except first substituting 7-acetyl-4-methyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (the R<sup>4</sup> reagent) from Step 273b for the R<sup>4</sup> reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H), 463 (1 Br); IR (cm<sup>-1</sup>) 3400, 3200-2800, 1700, 1640, 1605, 1590, 1395, 1380, 1345.

Example 274

4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

Step 274a. 7-acetyl-4-dimethylaminoethyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one

The compound from Example 273 Step a was treated with 2-chloro-(N,N-dimethyl)ethylamine HCl and K<sub>2</sub>CO<sub>3</sub> in aqueous acetone at reflux. The mixture was diluted with water and extracted with dichloromethane, and the residue was purified by chromatography to give the title compound.

Step 274b. 4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 244 Step c, except in step c first substituting 7-acetyl-4-dimethylaminoethyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (the R<sup>4</sup> reagent, from Step 273b) for the R<sup>4</sup> reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H), 519 (1 Br); IR (cm<sup>-1</sup>) 3440, 1685, 1630, 1605, 1580, 1395



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Example 275

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4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine

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Step 275a. 6-acetyl-2-benzoxazolinone

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Following the procedures of Example 273 Step a, except substituting 2-benzoxazolinone (Aldrich) for the 2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one thereof, the title compound was prepared.

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Step 275b. 6-acetyl-3-(dimethylaminoethyl)-2-benzoxazolinone

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The compound from Example 275 Step a was treated with 2-chloro-(N,N-dimethyl)ethylamine HCl and K<sub>2</sub>CO<sub>3</sub> in aqueous acetone at reflux. The mixture was diluted with water and extracted with dichloromethane, and the residue was purified by chromatography to give the title compound.

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Step 275c. 4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine

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Following the procedures of Example 244 Step c, except in step c first substituting the compound from Step 275a for the R<sup>4</sup> reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H), 506 (1 Br); IR (cm<sup>-1</sup>) 3400, 3050, 1630, 1610, 1360.

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## Example 276

4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

Step 276a. 6-acetyl-3-methyl-2-benzoxazolinone

The compound from Example 275 Step a was treated with methyl iodide and NaH in 1:1 THF/DMF for 6 hours at 0 °C to 25 °C. The reaction was quenched with aqueous sodium bicarbonate solution, the mixture was extracted with dichloromethane, and the residue was purified by chromatography to give the title compound.

Step 276b. 1-(3-hydroxy-4-methylaminophenyl)-ethanone

The compound from Step 276a (1.60 g, 8.37 mmol) was dissolved in acetone (70 mL) and treated with 1M aqueous K<sub>2</sub>CO<sub>3</sub> solution (25 mL) with heating at reflux overnight. The mixture was neutralized with acid, then extracted with diethyl ether. The solvent was dried (MgSO<sub>4</sub>) and removed under vacuum to give the title compound (2.01 g)

Step 276c. 7-acetyl-4-methyl-2H-4H-benzo-1,4-oxazin-3-one

The compound from Step 276b (2.01 g, 8.37 mmol) was dissolved in DMSO and treated with sodium ethoxide (8.4 mmol) and bromoacetic acid (1.40 g, 8.4 mmol) at room temperature overnight. The mixture was diluted with water and ether, and the title compound was isolated by filtration (0.48 g). MS (M+H), 206.

Step 276d. 4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 244 Step c, except in step c first substituting the compound from Step 276c for the R<sup>1</sup> reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was

prepared. MS (M+H), 462 (1 Br); IR (cm-1) 3500, 2800-3200, 1690, 1645, 1610, 1590, 1385, 1355.

#### Example 277

4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

##### Step 277a. 7-acetyl-2,2,4-trimethyl-2H-4H-benzo-1,4-oxazin-3-one

The compound from Step 276b (2.25 g, 9 mmol) was dissolved in DMSO and treated with sodium ethoxide (9 mmol) and 2-bromo-2-methylpropanoic acid (1.76 g, 9 mmol) at room temperature overnight. The mixture was diluted with water, and the mixture was extracted with ether.ethyl acetate. The extract was dried (MgSO<sub>4</sub>), the solvent was removed under vacuum, and the residue was purified by chromatography (silica gel) to give the title compound (1.33 g) MS (M+H), 234.

##### Step 277b. 4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 244 Step c, except in step c first substituting the compound from Step 277a for the R<sup>1</sup> reagent of Example 244 Step c, and secondly performing the condensation with ammonium acetate substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H), 490 (1 Br); IR (cm-1) 3450, 2900-3100, 1680, 1645, 1610, 1515, 1385, 1365, 1165.

#### Example 278

4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

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Step 278a. 1-(3-hydroxy-4-(2-(dimethylamino)ethyl)phenyl)-ethanone

A sample of 6-acetyl-3-(dimethylaminoethyl)-2-benzoxazolinone (from Example 275 Step b) was dissolved in acetone and treated with 1M aqueous K<sub>2</sub>CO<sub>3</sub> solution with heating at reflux overnight. The mixture was neutralized with acid, then extracted with diethyl ether. The solvent was dried (MgSO<sub>4</sub>) and removed under vacuum to give the title compound.

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Step 278b. 7-acetyl-4-(dimethylamino)ethyl-2H-4H-benzo-1,4-oxazin-3-one

A sample of the compound from Step 278a (8.94 g, 32 mmol) was dissolved in DMSO and treated with sodium ethoxide (32 mmol) and bromoacetic acid (5.34 g, 32 mmol) at room temperature for 2 days. The mixture was diluted with water then extracted with ether. The extract was dried (MgSO<sub>4</sub>), the solvent was removed under vacuum, and the residue was purified by chromatography (silica gel) to give the title compound (1.94 g). MS (M+H), 263.

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Step 278c. 4-amino-5-cyclohexyl-7-(4-(dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 244 Step c, except in step c first substituting 1,1-dicyano-3-cyclohexylethene (prepared according to the method of Moison, et al. (Tetrahedron (1987), 43:537-542) by treating cyclohexane carboxaldehyde with malononitrile in the presence of finely powdered magnesium oxide in dichloromethane) for the R<sup>3</sup> reagent of Example 244 Step c, and substituting the compound from Step 278b for the R<sup>4</sup> reagent of Example 244 Step c, and also performing the condensation with ammonium acetate but also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H) 447; IR(cm<sup>-1</sup>) 3400, 2900, 1690, 1610, 1590, 1395.

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Example 2794-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine

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Step 279a. 1-(5-methylethyl-2-pyridyl)ethanone

5 A solution of 2-acetyl-5-bromopyridine (1.45 g, 7.9 mmol), 2-propenyltrimethyltin (1.77 g, 8.7 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.33 g, 0.36 mmol), and tri-2-furylphosphine (0.17 g, 0.72 mmol) in 25 mL of benzene was warmed at 60 °C for 4 hours. The reaction mixture was concentrated and the coupled product was purified by flash chromatography (1.22 g, 96 %). The product was dissolved in 25 mL of EtOH and the solution was purged with a stream of H<sub>2</sub>. 10% Palladium on charcoal (50 mg) in 0.5 mL of EtOH was added and the reaction mixture was stirred for 12 h under an atmosphere of H<sub>2</sub>. The reaction mixture was filtered and the resulting solution was concentrated under reduced pressure. The title compound, 2, (1.04 g, 84%) was isolated following flash chromatography.

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15 Step 279b. 4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine

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Following the procedures of Example 244 Step c, except in step c substituting the compound from Step 279a for the R<sup>4</sup> reagent of Example 244 Step c, and performing the condensation with ammonium acetate and also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H) 421 (1Br); IR (cm<sup>-1</sup>) 3489, 2940, 1545, 1482, 1357.

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Examples 280-281

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25 Following the procedures of Example 244 Step c, except in step c substituting the compound shown below for the R<sup>4</sup> reagent of Example 244 Step c, and performing the condensation with ammonium acetate and also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds shown in the table below were prepared.

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| Ex. No. | Name  | R <sup>1</sup> Reagent (for 7-position)   | Analytical Data  |
|---------|---|---|--|
| 280     | 4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine       | 1-(5-piperidinyl-2-pyridyl)ethanone<br>*  | MS (M+H), 460 (1Br); IR (cm <sup>-1</sup> ) 3064, 2937, 1556, 1493, 1358       |
| 281     | 4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine | 1-(2-morpholinyl-5-pyridyl)ethanone<br>** | MS (M+H), 491 (1 Br); IR (cm <sup>-1</sup> ) 1585, 1555, 1505, 1240, 1110, 940 |

\* Prepared as in Ex. 252b, except substituting morpholine for the bis(2-methoxyethyl)amine thereof.

\*\* prepared by treatment of 5-acetyl-2-chloro-pyridine with morpholine in refluxing ethanol.

#### Example 282

4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine

#### 10 Step 282a. 4-cyanoacetophenone, acetal with 2,2-dimethylpropylene glycol

A sample of 4-cyanoacetophenone (4.35 g, 30 mmol) was dissolved in 150 mL of hexanes, and to this solution were added 2,2-dimethylpropylene glycol (3.44 g, 33 mmol) and a catalytic amount (10 mg) of p-toluene sulfonic acid. The reaction was heated overnight at reflux with a Dean-Stark trap, and an additional portion of glycol (33 mmol) was added. The reaction was continued for 3 hours, then cooled and the solvent was removed. The residue was dissolved in ethyl acetate, and this solution was washed with aqueous NaHCO<sub>3</sub>, water and brine, and dried over MgSO<sub>4</sub>. The solvent was removed under vacuum to give the title compound (7.46 g).

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Step 282b. 4-(aminomethyl)acetophenone, acetal with 2,2-dimethylpropylene glycol

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The compound from Step 282a (2.31 g, 10 mmol) was dissolved in ether (50 mL) and stirred with lithium aluminum hydride (0.76 g, 20 mmol) at ambient temperature overnight. The reaction was quenched with  $\text{MgSO}_4 \cdot 10 \text{H}_2\text{O}$ , and the mixture was diluted with ether. The mixture was filtered, and the filtrate removed to give the title compound.

15

Step 282c. 1-(4-(BOC-aminomethyl)phenyl)ethanone

20

The compound from Step 282b (1.18 g, 5 mmol) was dissolved in THF (20 mL), 1N HCl (20 mL) was added, and the mixture was stirred for 2 days. The volatiles were removed under vacuum, the residue was dissolved in THF (20 mL), and di-*t*-butyl dicarbonate (2.18 g, 10 mmol) was added. The mixture was stirred at room temperature over a weekend. The solution was diluted with water, and the mixture was extracted with ether and ethyl acetate. The organic extracts were dried ( $\text{MgSO}_4$ ), and the solvent was removed under vacuum to give the title compound.

25

15

Step 282d. 4-amino-5-(3-bromophenyl)-7-(4-(N-formylamino)methyl)phenylpyrido[2,3-d]pyrimidine

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Following the procedures of Example 244, except in step c substituting the compound from Step 282c for the  $\text{R}^1$  reagent of Example 244 Step c, and performing the condensation with ammonium acetate but also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS ( $\text{M}+\text{H}$ ) 434 (1 Br); IR ( $\text{cm}^{-1}$ ) 3440, 2700-3150, 1635, 1580, 1380.

35

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Example 2834-amino-5-(3-bromophenyl)-7-(4-(1-(N-methylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine

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50

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Step 283a. 4-(1-amino-1-methylethyl)acetophenone

CeCl<sub>3</sub> (10 g, 34.9 mmol) was suspended in THF (60 mL), and the mixture was cooled to -78 °C. Methyl lithium (1.4 M, 2 mL) was added, and the mixture was stirred for 20 minutes. Then the compound from Example 282 Step a, (4-cyanoacetophenone acetal with 2,2-dimethylpropylene glycol, 2.31 g, 10 mmol) in 2 mL of THF was added. After stirring for 4 hours, the mixture was allowed to warm to room temperature while stirring for 16 hours. The reaction was quenched with water and ammonium hydroxide, filtered, and the filtrate was extracted with dichloromethane. The solution was dried (MgSO<sub>4</sub>), and the solvent was removed to give the title compound.

Step 283b. 4-(1-(N-BOC-amino)-1-methylethyl)acetophenone

The compound from Step 283a (2.32 g, 8.77 mmol) was treated sequentially with HCl and di-t-butyl dicarbonate according to the procedure of Example 282 Step c to give the title compound (1.60 g). MS (M+H) 278.

Step 283c. 4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 244 Step c, except in step c substituting the compound from Step 283b for the R<sup>1</sup> reagent of Example 244 Step c, and performing the condensation with ammonium acetate but also substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the title compound was prepared. MS (M+H) 462 (1 Br); IR (cm<sup>-1</sup>) 3440, 1640, 1605, 1580, 1380.

Example 284

4-amino-5-(3-bromophenyl)-7-(4-(1-(N,N-dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine



Step 284a. 4-(1-(dimethylamino)-1-methylethyl)acetophenone

The compound from Step 283a (1.18 g, 5 mmol) was dissolved in 5 mL formic acid, and 5 mL of formalin (37% ) was added. The mixture was heated at reflux for 4 hours, then cooled and neutralized with 2N Na<sub>2</sub>CO<sub>3</sub>. The mixture was extracted with dichloromethane. The solution was dried (MgSO<sub>4</sub>), and the solvent was removed to give the title compound (0.94 g). MS (M+H) 462 (1 Br); IR (cm<sup>-1</sup>) 3520, 1640, 1610, 1580, 1375.

Examples 285-286

Following the procedures of Example 157, except substituting the appropriate reagents for the R<sup>3</sup> and R<sup>4</sup> reagents of Example 157 as indicated in the Table below, compounds of Examples 285-286 were prepared. For Example 286, treatment with aqueous HCl was omitted, and the free base was obtained.

Examples 285-286

| Ex. No. | Name  | R <sup>3</sup> Reagent (for 5-position) | R <sup>4</sup> Reagent (for 7-position) | Analytical Data  |
|---------|---|---|---|--|
| 285     | 4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-(3-(3-bromophenyl)propene   | 1-(N-acetyl-5-indolyl)-ethanone         | mp (hydrochloride salt ) >270°C. IR (cm <sup>-1</sup> ) 3445, 3100-2500, 1640, 1605, 1445, 1395, 1325. LRMS [M+H] <sup>+</sup> m/z 460, 462. |

|     |  |                                |                                 |   |
|-----|--|--------------------------------|---------------------------------|---|
| 286 | 4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-3-cyclohexylethene | 1-(6-chloro-3-pyridyl)-ethanone | mp 240-242 °C. IR (cm-1) 3528, 3300, 3086, 2936, 2853, 1645, 1590, 1575, 1565, 1350. LRMS [M+H] <sup>+</sup> m/z 340. |
|-----|--|--------------------------------|---------------------------------|---|

#### Examples 287-300

Following the procedures of Example 157, except substituting the appropriate R<sup>3</sup> and R<sup>4</sup> reagents as indicated in the Table below and replacing the formamide or formamidine acetate treatment with treatment with triethyl orthoformate at reflux in the presence of a catalytic amount of ammonium sulfate, followed by cooling to 25 °C and addition of excess ammonia in ethanol, compounds of Examples 287-300 were prepared. After 24 hours, the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichloroethane at reflux for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary. The treatment with aqueous HCl was omitted in some cases, and the free bases were obtained.

#### Examples 287-300

| Ex. No. | Name  | R <sup>3</sup> Reagent (for 5-position)        | R <sup>4</sup> Reagent (for 7-position) | Analytical Data  |
|---------|---|--|---|--|
| 287     | 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-2-methyl-(3-(2-bromophenyl)propene | 1-(6-dimethylamino-3-pyridyl)-ethanone  | IR (cm-1) 2600-3500, 1650, 1602, 1596, 1520 cm-1. LRMS [M+H] <sup>+</sup> m/z 449,451. |

|     |   |  |  |   |
|-----|---|--|--|---|
| 288 | 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine             | 1,1-dicyano-2-methyl-(3-(2-bromophenyl)propene | 1-(6-morpholinyl-3-pyridyl)-ethanone               | mp (dihydrochloride salt) 213-216 °C. IR (cm <sup>-1</sup> ) 2400-3500, 1660, 1600. LRMS [M+H] <sup>+</sup> m/z 491 & 493.                |
| 289 | 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-(N-methyl-N-formyl)amino)-3-phenylpyrido[2,3-d]pyrimidine | 1,1-dicyano-2-methyl-(3-(2-bromophenyl)propene | 1-(6-(N-methyl-N-formyl)amino)-3-pyridyl)-ethanone | mp 252-253°C. IR (cm <sup>-1</sup> ) 3515, 3310, 3200-2800, 1675, 1585, 1560, 1545, 1340. LRMS [M+H] <sup>+</sup> m/z 462, 464.           |
| 290 | 4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine                           | 1,1-dicyano-3-cyclohexylethene                 | 1-(6-morpholinyl-3-pyridyl)-ethanone               | mp (dihydrochloride salt) 208-210. IR (cm <sup>-1</sup> ) 3490, 3300, 3050-3250, 1620, 1580, 1550, 1490. LRMS [M+H] <sup>+</sup> m/z 391. |

|     |  |  |  |   |
|-----|--|--|--|---|
| 291 | 4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-3-(2-bromophenyl)propene             | 1-(6-morpholinyl-3-pyridyl)-ethanone   | mp<br>(dihydrochloride salt) 201-204 °C.<br>IR (cm-1) 3601, 3500, 3310, 2960, 2850, 1585, 1561, 1502, 1345<br>LRMS [M+H] <sup>+</sup> m/z 477, 479.   |
| 292 | 4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine   | 1,1-dicyano-3-(4-tetrahydropyranylyl)ethene<br>* | 1-(6-morpholinyl-3-pyridyl)-ethanone   | mp<br>(dihydrochloride salt) 213-216 °C.<br>IR (cm-1) 3310, 3060, 2955, 1587, 1559, 1506, 1350.<br>LRMS [M+H] <sup>+</sup> m/z 393.                   |
| 293 | 4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine            | 1,1-dicyano-3-cyclohexylethene                   | 1-(6-dimethylamino-3-pyridyl)-ethanone | mp<br>(dihydrochloride salt) 272-274 °C.<br>IR (cm-1) 3532, 3294, 3100, 2930, 2853, 1606, 1586, 1560, 1522, 1387.<br>LRMS [M+H] <sup>+</sup> m/z 349. |

|     |   |  |  |   |
|-----|---|--|--|---|
| 294 | 4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine          | 1,1-dicyano-3-ethylpentene                   | 1-(6-dimethylamino-3-pyridyl)-ethanone | mp (free base): 223.5-225 °C. IR (cm <sup>-1</sup> ) 3480, 3000-3470, 2800-3000, 1630, 1610, 1580, 1565, 1520. LRMS [M+H] <sup>+</sup> m/z 337. |
| 295 | 4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine                | 1,1-dicyano-3-cyclopentylethene              | 1-(6-morpholinyl-3-pyridyl)-ethanone   | IR (cm <sup>-1</sup> ) 3495, 3320, 3080, 2950, 1645, 1600, 1500, 1400, 1350, 1240. LRMS [M+H] <sup>+</sup> m/z 377.                             |
| 296 | 4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine                      | 1,1-dicyano-3-cyclohexylethene               | 1-(2-chloro-3-pyridyl)-ethanone        | IR (cm <sup>-1</sup> ) 3305, 3155, 2930, 2855, 1590, 1610, 1590, 1545, 1345. LRMS [M+H] <sup>+</sup> m/z 340, 342.                              |
| 297 | 4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-3-(3,5-dimethylcyclohexyl)ethene | 1-(6-dimethylamino-3-pyridyl)-ethanone | IR (cm <sup>-1</sup> ) 3310, 3100, 2950, 1605, 1590, 1555, 1390, 1350. LRMS [M+H] <sup>+</sup> m/z 377.   |

|     |  |  |                                      |  |
|-----|--|--|--------------------------------------|--|
| 298 | 4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-3-(4-(benzyloxycarbonyl)piperidin-1-yl)propene | 1-(6-morpholinyl-3-pyridyl)-ethanone | IR (cm-1) 3538, 3311, 3032, 2925, 2852, 1696, 1585, 1560. LRMS [M+H] <sup>+</sup> m/z 540.                                     |
| 299 | 4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine  | 1,1-dicyano-3-cyclohexylethene                             | 1-(6-bromo-3-pyridyl)-ethanone       | m.p. 250-252 °C, IR (cm-1) 3530, 3298, 3093, 2932, 2856, 1645, 1583, 1569, 1543, 1461, 1346. LRMS [M+H] <sup>+</sup> 384, 386. |
| 300 | 4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine  | 1,1-dicyano-3-cyclohexylethene                             | 1-(3-cyanophenyl)-ethanone           | m. p. 223-224 °C. IR (cm-1) 3528, 3298, 3075, 2937, 2235, 1645, 1586, 1548, 1567, 1463. LRMS [M+H] <sup>+</sup> 332.           |

\* The 1,1-dicyano-3-cyclohexylethene was prepared according to the method of Moison, et al. (Tetrahedron (1987), 43:537-542) by treating cyclohexane carboxaldehyde with malononitrile in the presence of finely powdered magnesium oxide in dichloromethane.

The reagents for the following examples were prepared by this method substituting the compound shown below for the cyclohexane carboxaldehyde used to prepare the reagent of Example 290.

Example 292. tetrahydropyran-4-carboxaldehyde;

Example 294. 2-ethylbutanaldehyde;

Example 295, cyclopentane carboxaldehyde;

Example 297, 3,5-dimethylcyclohexane carboxaldehyde;

Example 298, N-(phenylmethoxycarbonyl)piperidine-4-carboxaldehyde

(this material was prepared from N-(carbobenzyloxy)-4-(2-hydroxyethyl)piperidine (Brehm et al., *Helv.Chim.Acta*, 70; (1987), 1981-1987 by treatment with TEMPO (2,2,6,6-tetramethylpiperidinyloxy radical) and potassium bromide in dichloromethane at 0 °C to which was added commercial bleach (Clorox) containing sodium bicarbonate).

#### Examples 301-305

Following the procedures of Example 246, except in step (c) substituting the appropriate reagents for methylamine as indicated in the Table below to prepare the correct R<sup>4</sup> reagent, and substituting the R<sup>3</sup> reagent shown below for the R<sup>3</sup> reagent of Example 246 step d, the compounds of Examples 301-305 were prepared. For Example 302 only, the condensation solvent was DMSO instead of ethanol and dimethoxyethane.

#### Examples 301-305

| Ex. No. | Name  | R <sup>3</sup> reagent                | reagent of step c | Analytical Data   |
|---------|---|---------------------------------------|-------------------|---|
| 301     | 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-(3-(2-bromophenyl)propene | dimethylamine     | mp<br>(dihydrochloride salt) >220°C.<br>IR (cm <sup>-1</sup> ) 3500-2400, 1640, 1610, 1580, 1370. LRMS [M+H] <sup>+</sup> m/z 450, 452. |

|     |   |                               |                                 |   |
|-----|---|-------------------------------|---------------------------------|---|
| 302 | 4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine                         | 1',1'-dicyano-(3-bromostyrene | imidazole sodium salt           | mp (tetrahydrochloride salt) >240°C. IR (cm <sup>-1</sup> ) 3600-2400, 1640, 1610, 1590, 1560, 1415, 1370. LRMS [M+H] <sup>+</sup> m/z 445, 447.    |
| 303 | 4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine                 | 1',1'-dicyano-(3-bromostyrene | azacycloheptane                 | mp (dihydrochloride salt) >190°C. IR (cm <sup>-1</sup> ) 3435, 3100-2400, 1635, 1610, 1590, 1550, 1440, 1370. LRMS [M+H] <sup>+</sup> m/z 476, 478. |
| 304 | 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine | 1',1'-dicyano-(3-bromostyrene | N-methyl-N-(1-methylethyl)amine | mp (dihydrochloride salt) >210°C. IR (cm <sup>-1</sup> ) 3435, 3100-2400, 1635, 1610, 1590, 1550, 1410, 1370. LRMS [M+H] <sup>+</sup> m/z 450, 452. |



|     |   |                                       |            |  |
|-----|---|---------------------------------------|------------|--|
| 305 | 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine | 1,1-dicyano-(3-(2-bromophenyl)propene | morpholine | IR (cm-1) 3475, 3313, 3100, 1650, 1620, 1580, 1555. LRMS [M+H] <sup>+</sup> at 492, 494. |
|-----|---|---------------------------------------|------------|--|

Example 3064-amino-5-cyclohexyl-7-(6-(4-acetylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

A mixture of 679 mg (2 mmol) of the compound from Example 298 and 1.28 g (10 mmol) of N-acetylpiperazine in 5 mL of DMSO was heated at 110 °C for 5 hours. On cooling a precipitate was deposited, which was collected and washed with 20% methanol and dried to give 647 mg of the product as orange flakes: IR (cm-1) 3522, 3306, 3110, 2925, 2854, 1670, 1650, 1586, 1506. LRMS [M+H]<sup>+</sup> m/z 432.

Examples 307-322

Following the procedure of Example 306, except substituting the reagent shown in the table below for the N-acetylpiperazine of Example 306, the compounds shown in the table were prepared. The compounds were purified by HPLC chromatography.

| Ex. No. | Name | reagent | Analytical Data |
|---------|------|---------|-----------------|
|---------|------|---------|-----------------|

|      |   |   |   |
|------|---|---|---|
| 307  | 4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine               | 1-acetyl-1,4-diazacycloheptane              | m.p. 169-171 °C, IR (cm-1) 3535, 3309, 3096, 2930, 2854, 1638, 1605, 1587, 1558, 1513. LRMS [M+H] <sup>+</sup> 446. |
| 308  | 4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine               | 1-methyl-1,4-diazacycloheptane              | LRMS [M+H] <sup>+</sup> 419.  |
| 309  | 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine          | N-methyl-N-(2-(2-pyridyl)ethyl)amine        | LRMS [M+H] <sup>+</sup> 441.  |
| 3101 | 4-amino-5-cyclohexyl-7-(6-(2-(N-(N',N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine | N,N-dimethyl, N'-methyl-1,2-ethylenediamine | LRMS [M+H] <sup>+</sup> 421.  |

|     |   |  |                              |
|-----|---|--|------------------------------|
| 311 | 4-amino-5-cyclohexyl-7-(6-azetidiny-3-pyridyl)pyrido[2,3-d]pyrimidine                           | azetidine                                  | LRMS [M+H] <sup>+</sup> 361. |
| 312 | 4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine    | N-methyl-N-(3-pyrrolidinyl)acetamide       | LRMS [M+H] <sup>+</sup> 447. |
| 313 | 4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine            | pyrrolidine-2-formamide                    | LRMS [M+H] <sup>+</sup> 419. |
| 314 | 4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrido[2,3-d]pyrimidine | 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one | LRMS [M+H] <sup>+</sup> 536. |
| 315 | 4-amino-5-cyclohexyl-7-(6-(2-(methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine     | 2-(methoxymethyl)pyrrolidine               | LRMS [M+H] <sup>+</sup> 420. |

|     |   |                                      |                              |
|-----|---|--------------------------------------|------------------------------|
| 316 | 4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine | N-(methoxyethyl)propylamine          | LRMS [M+H] <sup>+</sup> 421. |
| 317 | 4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine    | 2-(methylamino)-dimethylacetaldehyde | LRMS [M+H] <sup>+</sup> 429. |
| 318 | 4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine | N-(4-piperidyl)-dimethylamine        | LRMS [M+H] <sup>+</sup> 433. |
| 319 | 4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine | piperidine-4-formamide               | LRMS [M+H] <sup>+</sup> 433. |

|     |  |  |                              |
|-----|--|--|------------------------------|
| 320 | 4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine | N <sup>1</sup> , N <sup>1</sup> -diethyl-N <sup>1</sup> -methyl-1,3-propanediamine | LRMS [M+H] <sup>+</sup> 449. |
| 321 | 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine     | N-methyl-(4-pyridyl)ethylamine   | LRMS [M+H] <sup>+</sup> 441. |
| 322 | 4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)pyrid-3-yl)pyrido[2,3-d]pyrimidine    | N-methyl-(3-pyridyl)methylamine  | LRMS [M+H] <sup>+</sup> 427. |

#### Example 323

##### 4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine

The procedures of Example 157 were followed, except substituting 1',1'-dicyano-3-bromostyrene for the R<sup>3</sup> reagent and 1-(1-methyl-5-indolyl)-ethanone for the R<sup>4</sup> reagent. After 24 hours, the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichloroethane at reflux for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary. The treatment with

aqueous HCl was omitted, and the free bases was obtained. IR (KBr)  $\text{cm}^{-1}$  3500, 1578, 1500; MS  $m/z$  431 ( $M+H$ ) $^{+}$ .

#### Example 324

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 323 by oxidation with  $\text{CrO}_3$  in sulfuric acid. IR (microscope) 3471, 1765, 1500  $\text{cm}^{-1}$ ; MS  $m/z$  461( $M+H$ ) $^{+}$ .

#### Examples 325-326

Following the procedures of Example 157, except substituting the appropriate  $R^3$  and  $R^4$  reagents as indicated in the Table below, compounds of Examples 325-326 were prepared. After 24 hours, the precipitated amidine compound was filtered and washed with hexanes, then dried under vacuum. The amidine compound was then heated in 1,2-dichloroethane at reflux for 1-8 hours. The reaction mixture was cooled to room temperature and purified by chromatography, and the product was recrystallized if necessary. The treatment with aqueous HCl was omitted in some cases, and the free bases were obtained.

#### Examples 325-326

| Ex. No. | Name  | $R^3$ Reagent (for 5-position) | $R^4$ Reagent (for 7-position)                 | Analytical Data   |
|---------|---|--------------------------------|--|---|
| 325     | 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine | 1',1'-dicyano-3-bromostyrene   | 1-(3-fluoro-4-(1-morpholinyl)phe-nyl)-ethanone | IR (microscope) 3443, 3044, 1639, 1606, 1584, 1520, 1362, 1245 $\text{cm}^{-1}$ ; MS $m/z$ 480 ( $M+H$ ) $^{+}$ . |

|     |  |                              |                                      |  |
|-----|--|------------------------------|--------------------------------------|--|
| 326 | 4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine | 1',1'-dicyano-3-bromostyrene | 1-(4-hydroxy-3-nitrophenyl)-ethanone | IR (KBr) 3461, 1623, 1579, 1548, 1523, 1353 cm <sup>-1</sup> ; MS m/z 438 (M+H) <sup>+</sup> . |
|-----|--|------------------------------|--------------------------------------|--|

Example 327

Following the procedures of Example 244 Step c, except in step c substituting the compound resulting from the reaction of 2-acetyl-5-chloropyridine in refluxing ethanol with the precursor reagent compound (4-piperidinone ethylene ketal) shown below for the R<sup>4</sup> reagent of Example 244 Step c, and substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compound shown in the table below was prepared.

| Ex. No. | Name   | precursor reagent             | Analytical Data   |
|---------|--|-------------------------------|---|
| 327     | 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine | 4-piperidinone ethylene ketal | IR (microscope) 3091, 1602, 1580, 1558, 1512, 1353, 1236, 1103 cm <sup>-1</sup> ; MS m/z 519 (M+H) <sup>+</sup> . |

Example 328

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Treating the compound of Example 327 with dilute HCl, the title compound was prepared. IR (microscope) 3438, 3051, 1645, 1605, 1558, 1450, 1371, 1240 cm<sup>-1</sup>; MS m/z 475 (M+H)<sup>+</sup>.

5

Examples 329-331

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Following the procedures of Example 327, except in step c substituting the precursor reagent compound shown below for the R<sup>1</sup> reagent of Example 244 Step c, and substituting dichloroethane as the solvent in place of the ethanol solvent in Example 244 step c, the compounds shown in the table below were prepared.

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Examples 329-331

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| Ex. No. | Name   | precursor reagent  | Analytical Data  |
|---------|--|--------------------|--|
| 329     | 4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine | piperazine         | IR (KBr) 3489, 1674, 1602, 1581, 1559, 1503, 1233, 1004 cm <sup>-1</sup> ; MS m/z 491 (M+H) <sup>+</sup> . |
| 330     | 4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine | 1-methylpiperazine | IR (microscope) 3438, 3051, 1540 cm <sup>-1</sup> ; MS m/z 477 (M+H) <sup>+</sup> .                        |
| 331     | 4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidin        | thiomorpholine     | IR (KBr) 3486, 1602, 1581, 1560, 1502, 1228 cm <sup>-1</sup> ; MS m/z 479 (M+H) <sup>+</sup> .             |

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Example 3324-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

The compound of Example 331 was treated with 4-chloroperbenzoic acid in methanol and dichloromethane to give the title compound. IR (microscope) 3471, 1601, 1581, 1562, 1510, 1353, 1316, 1285, 1122 cm<sup>-1</sup>; MS m/z 511(M+H)<sup>+</sup>.

Example 3334-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidineStep 333a. 1',1'-dicyano-2-bromostyrene

The title compound was prepared by condensation of 2-bromobenzaldehyde with malononitrile and MgO in dichloromethane by the standard procedure of Broekhuis et al. (Recl. J. R. Neth. Chem. Soc., 99: 6-12 (1980)).

Step 333b. 5-acetyl-2-morpholinylpyridine

The title compound was prepared by the reaction of 5-acetyl-2-chloropyridine with morpholine in refluxing ethanol.

Step 333c. 4-(2-bromophenyl)-3-cyano-6-morpholinylpyridine-2-amine

The title compound was prepared by condensation of 1',1'-dicyano-2-bromostyrene with 5-acetyl-2-morpholinylpyridine and ammonium acetate in dichloroethane at reflux. After the reaction was complete (TLC), the mixture was cooled, and the solvent was removed. The residue was triturated with methanol to give the product.

Step 333d. 4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

A sample of 4-(2-bromophenyl)-3-cyano-6-morpholinylpyridine-2-amine was heated at 180-190 °C in formamide. The reaction was monitored by TLC, and when the reaction was complete the mixture was cooled to room temperature. The product was

allowed to precipitate, then recovered by filtration and washed with water. Additional product was extracted from the filtrate. The product was purified by column chromatography eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. IR (microscope) 3493, 1547, 1109cm<sup>-1</sup>; MS m/z 464 (M+H)<sup>+</sup>.

5

Examples 334-336

Following the procedures of Example 333, except in Step a substituting the precursor aldehyde reagent shown below for the 2-bromobenzaldehyde of Example 333 Step a, and carrying the product forward as in procedures 333 Steps b-d, the compounds shown in the table below were prepared.

Examples 334-336

| Ex. No. | Name   | precursor aldehyde reagent    | Analytical Data   |
|---------|--|-------------------------------|---|
| 334     | 4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine | 3-bromo-4-methoxybenzaldehyde | IR (microscope) 3486, 1600, 1575, 1562, 1500, 1260, 1237 cm <sup>-1</sup> ; MS m/z 493 (M+H) <sup>+</sup> . |
| 335     | 4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine           | 4-bromobenzaldehyde           | IR (microscope) 3497, 1532, 1098cm <sup>-1</sup> ; MS m/z 464 (M+H) <sup>+</sup> .                          |

|     |   |                      |   |
|-----|---|----------------------|---|
| 336 | 4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine | 3-chlorobenzaldehyde | IR (microscope) 3484, 1500, 1034 $\text{cm}^{-1}$ ; MS (FAB) $m/z$ 587 (M+H) $^{+}$ . |
|-----|---|----------------------|---|

Example 3374-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Following the procedures of Example 333, except in Step a substituting 3-bromobenzaldehyde for the 2-bromobenzaldehyde, in Step b substituting 5-acetyl-2,3-dichloropyridine for the 5-acetyl-2-chloropyridine to give 5-acetyl-3-chloro-2-morpholinylpyridine, and substituting 5-acetyl-3-chloro-2-morpholinylpyridine for the 5-acetyl-2-morpholinylpyridine in step c, then the carrying the product forward as in Example 333 Step d, the title compound was prepared. IR (microscope) 3493, 1635, 1585, 1555, 1492, 1340, 1241, 1113  $\text{cm}^{-1}$ ; MS  $m/z$  497 (M+H) $^{+}$ .

Example 3384-amino-5-(3-bromophenyl)-7-(6-(N-oxido-morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared by treating the compound of Example 134 with hydrogen peroxide in acetic acid according to standard procedures. IR (microscope) 3486, 1579, 1552, 1353, 1121, 1020  $\text{cm}^{-1}$ ; MS  $m/z$  479 (M+H) $^{+}$ .

5

Example 339

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-ethoxyethyl)amino)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

10

5 Step 339a. 1',1'-dicyano-3-bromostyrene

15

The title compound was prepared by condensation of 3-bromobenzaldehyde with malononitrile and MgO in dichloromethane by the standard procedure of Broekhuis et al. (Recl. J. R. Neth. Chem. Soc., 99: 6-12 (1980)).

20

10 Step 339b. 5-acetyl-2-(N-(2-ethoxyethyl)amino)pyridine

The title compound was prepared by the reaction of 5-acetyl-2-chloropyridine with 2-ethoxyethylamine in refluxing ethanol.

25

Step 339c. 4-(3-bromophenyl)-3-cyano-6-(N-(2-ethoxyethyl)amino)pyridine-2-amine

30

15 The title compound was prepared by condensation of 1',1'-dicyano-2-bromostyrene with 5-acetyl-2-morpholinylpyridine and ammonium acetate in dichloroethane at reflux. After the reaction was complete (TLC), the mixture was cooled, and the solvent was removed. The residue was triturated with methanol to give the product.

35

20 Step 339d. 4-amino-5-(2-bromophenyl)-7-(6-(N-(2-ethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

40

25 A sample of the compound from Step 239d was treated according to the procedure of Example 233d to give the title compound. IR (microscope) 3301, 1610, 1579, 1543, 1346, 1304, 1120  $\text{cm}^{-1}$ ; MS  $m/z$  481 (M+H)<sup>+</sup>.

45

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Example 340

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine

10

This compound was isolated by chromatography as a product of the reaction described in Example 239 Step d. IR (microscope) 3306, 1679, 1596, 1577, 1548, 1493, 1352, 1125 cm<sup>-1</sup>; MS m/z 509 (M+H)<sup>+</sup>.

15

Example 341

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl)-N-oxide)pyrido[2,3-d]pyrimidine

10

20

The title compound was prepared by treating the compound of Example 341 with hydrogen peroxide in acetic acid according to standard procedures. IR (microscope) 3296, 1628, 1560, 1411, 1353 cm<sup>-1</sup>; MS m/z 497 (M+H)<sup>+</sup>.

25

15

Example 342

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

20

The title compound was prepared from the compound of Example 328 by reduction with (Lithium Aluminum Hydride, and subsequent workup according to standard procedures). IR (microscope) 3349, 1510, 1116 cm<sup>-1</sup>; MS m/z 478 (M+H)<sup>+</sup>.

35

Example 343

1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt

40

25

The title compound was prepared from the compound of Example 342 by treatment with POCl<sub>3</sub>, and subsequent workup according to standard procedures. IR (microscope) 3498, 1500, 1444 cm<sup>-1</sup>; MS m/z 556 (M+H)<sup>+</sup>.

45

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Example 344

4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

10

The title compound was prepared from the compound of Example 339 by  
5 oxidation of the free hydroxy group to an aldehyde with TEMPO reagent. During workup  
of the mixture, the compound self-condensed to give the title compound.

15

MS m/z 492 (M+CH<sub>3</sub>OH-H<sub>2</sub>O)<sup>+</sup>.

Example 345

10 4-amino-5-(3-bromophenyl)-7-(4-methylenylpiperidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

20

The title compound was prepared from the compound of Example 328 by  
treatment with methyl triphenylphosphine bromide at -78 °C in DMSO. After quenching  
25 and warming the mixture to room temperature, the title compound was extracted, then  
15 purified by chromatography. IR (microscope) 3055, 1602, 1559, 1508, 1440, 1344, 1174  
cm<sup>-1</sup>; MS m/z 473 (M+H)<sup>+</sup>.

30

Example 346

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine

20

35

The title compound was prepared from the compound of Example 345 by  
treatment with OsO<sub>4</sub> in DMSO at room temperature. After quenching, the title compound  
was extracted, then purified by chromatography. IR (microscope) 3304, 1603, 1580,  
1557, 1509, 1352, 1241 cm<sup>-1</sup>; MS m/z 507 (M+H)<sup>+</sup>.

40

25

Example 347

4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

45

30 Step 347a. 1,1-dicyano-3-cyclohexylethene

50

55

5 The 1,1-dicyano-3-cyclohexylethene was prepared according to the method of Moison, et al. (Tetrahedron (1987), 43:537-542) by treating cyclohexane carboxaldehyde  
10 with malononitrile in the presence of finely powdered magnesium oxide in dichloromethane.

5 Step 347b. 2-acetyl-5-(4,4-ethylenedioxy-piperidinyl)-pyridine

15 A sample of 2-acetyl-5-chloropyridine was treated in refluxing ethanol with 4-piperidinone ethylene ketal to give the title compound.

10 Step 347c. 4-amino-5-cyclohexyl-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20 Following the procedures of example 339 Step c, except substituting the compounds from Step 347a and 347b for the compounds of Steps 339a and 339b, and carrying the product forward according to the procedure of example 339 Step d, the title  
25 compound was prepared. IR (microscope) 2929, 1604, 1585, 1557, 1514, 1426, 1344, 1238, 1106 cm<sup>-1</sup>; MS m/z 447 (M+H)<sup>+</sup>.

30 Example 348

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20 The title compound was prepared from the compound of Example 347 by treatment with dilute HCl in ethanol. The title compound was purified by  
35 chromatography. IR (microscope) 2928, 1715, 1603, 1585, 1559, 1507, 1344, 1226 cm<sup>-1</sup>; MS m/z 403 (M+H)<sup>+</sup>.

40 Example 349

25 4-amino-5-cyclohexyl-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared from the compound of Example 348 by  
45 treatment with methyl triphenylphosphine bromide at -78 °C in DMSO. After quenching and warming the mixture to room temperature, the title compound was extracted, then

purified by chromatography. IR (microscope) 2929, 1604, 1584, 1557, 1506, 1342, 1239  $\text{cm}^{-1}$ ; MS  $m/z$  401 (M+H)<sup>+</sup>.

#### Example 350

4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine

This compound was isolated from the reaction mixture of Example 293 as a side product: IR ( $\text{cm}^{-1}$ ) 3289, 3089, 2930, 2841, 1674, 1606, 1559, 1531. LRMS [M+H]<sup>+</sup>  $m/z$  376.

#### Example 351

(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethyl)pyrrolidinyl)-3-pyridinylpyrido[2,3-d]pyrimidine

Prepared as described for Examples 2-156; using (S)-1-(6-(O-methyl-2-pyrrolidinemethanol)-3-pyridinyl)ethanone as R<sub>1</sub> reagent (for position 7) and 3-bromobenzaldehyde for R<sub>3</sub> reagent (for 5-position).

MS (ESI(+)) 489/491 (M+H)<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br;

IR (KBr pellet)  $\nu_{\text{max}}$  3484, 3203, 1603, 1581, 1556  $\text{cm}^{-1}$ .

#### Example 352

(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxyethyl)pyrrolidinyl)-3-pyridinylpyrido[2,3-d]pyrimidine

Prepared as described for Examples 2-156; using (S)-1-(6-(2-pyrrolidinemethanol)-3-pyridinyl)ethanone as R<sub>1</sub> reagent (for position 7) and 3-bromobenzaldehyde for R<sub>3</sub> reagent (for 5-position).

MS (ESI(+)) 477/479 (M+H)<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br;

IR (KBr pellet)  $\nu_{\text{max}}$  3487, 3303, 3208, 2949, 1605, 1577, 1558, 1510, 1415, 1351, 1244, 1158, 828, 704  $\text{cm}^{-1}$ .

#### Example 353



4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-  
d]pyrimidine

Prepared as described for Examples 2-156, using 1-(6-(4-hydroxypiperidine)-3-pyridinyl)ethanone as R<sub>1</sub> reagent (for position 7) and 2-bromobenzaldehyde for R<sub>2</sub> reagent (for 5-position).

MS (ESI(+)) 477/479 (M+H<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br);

IR (KBr pellet)  $\nu_{\max}$  3485, 3298, 3198, 2938, 2848, 1600, 1574, 1557, 1351, 1225, 1024, 766 cm<sup>-1</sup>.

Example 354

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridinyl)pyrido[2,3-  
d]pyrimidine

Prepared as described for Example 327: using 4-fluorobenzaldehyde instead of 3-bromobenzaldehyde as precursor reagent as described in example 244 Step C.

MS (ESI(+)) 459 (M+H<sup>+</sup>);

IR (KBr pellet)  $\nu_{\max}$  3487, 3299, 3066, 1959, 1604, 1577, 1559, 1510, 1355, 1235, 1107, 943, 897, 792 cm<sup>-1</sup>.

Example 355

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-  
d]pyrimidine

Prepared as described for Examples 301-305, using 4-hydroxypiperidine as reagent for Step C (to prepare correct R<sub>1</sub> reagent).

MS (ESI(+)) 478/480 (M+H<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br);

IR (KBr pellet)  $\nu_{\max}$  3487, 3312, 1576, 1549, 1486, 1353, 1081 cm<sup>-1</sup>.

Example 356

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridazyl)pyrido[2,3-  
d]pyrimidine

Prepared as described for Examples 301-305: using 4-piperidinone ethylene ketal

as reagent for Step C (to prepare correct R<sub>1</sub> reagent).

MS (ESI(+)) 520/522 (M+H<sup>+</sup>; <sup>79</sup>Br<sup>81</sup>Br);

IR (KBr pellet)  $\nu_{\text{max}}$  3476, 3297, 1574, 1561, 1461, 1354, 1145, 1103 cm<sup>-1</sup>.

#### Example 357

##### 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine

A solution of the product from 357d (2.49 g, 5.30 mmol) in o-dichlorobenzene (15 mL) was heated to reflux overnight. The reaction mixture was cooled to room temperature, the solid collected by filtration and purified by silica gel chromatography (elution with 3% methanol:dichloromethane) to provide 1.06 g (43%) of the desired title product as a yellow solid. mp: >280 °C; MS (DCI/NH<sub>3</sub>) m/z 469/471 (M+H)<sup>+</sup>; IR (microscope) 3481, 2046, 1506, 1491, 1116 cm<sup>-1</sup>.

##### 357a: 2-morpholinylthiazole

2-bromothiazole (12.63 g, 77.00 mmol) in morpholine (30.0 mL) was sealed into a tube and heated to 100 °C for 3 days. The mixture was cooled, partitioned between water and dichloromethane, the layers separated and the organic phase dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 12.5 g (95%) of the desired compound as a brown oil. Material used directly in the next reaction. MS (DCI/NH<sub>3</sub>) m/z 171 (M+H)<sup>+</sup>.

##### 357b: 5-acetyl-2-morpholinylthiazole

A solution of the product from Example 357a (7.20 g, 42.3 mmol) in tetrahydrofuran (80 mL) at -78 °C was treated with N-BuLi (2 M in hexanes, 23.5 mL). After 30 minutes, the reaction mixture was transferred via cannula to a solution of acetic anhydride (10 mL) in tetrahydrofuran (50 mL) at -60 °C and stirred for 1 hour. The slurry was then warmed to room temperature for an additional 30 minutes, quenched with saturated sodium bicarbonate and extracted with diethyl ether. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and purified by silica gel chromatography (elution with 50% dichloromethane/ethyl acetate) to provide 3.70 g (41%) of the desired compound. MS (DCI/NH<sub>3</sub>) m/z 213 (M+H)<sup>+</sup>.

5

357c: 4-(3-Bromophenyl)-3-cyano-6-(2-morpholinethiazolo)pyridine-2-amine

10

A slurry of the product from 357b (4.91 g, 23.1 mmol) and ammonium acetate (9.75 g, 127 mmol) in 1,2-dichloroethane (50 mL) was treated with 2-(3-bromobenzylidene)malononitrile (10.78 g, 46.3 mmol; J. Am. Chem. Soc. 1949, 71, 2949) and the mixture heated to reflux overnight. The solution was cooled to room temperature, hexanes (50 mL) added and stirring continued for 3 hours. The solid was collected by filtration, washed with methanol and dried to provide 4.57 g (45%) of the desired material as an orange solid. MS (DCI/NH<sub>3</sub>) m/z 442/444 (M+H)<sup>+</sup>.

15

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357d: 4-(3-Bromophenyl)-3-cyano-6-(2-morpholinethiazolo)pyridine-2-amidine

25

15

A solution of the product from 357c (1.50 g, 3.39 mmol) and triethylorthoformate (34 mL) with a catalytic amount of ammonium sulfate was heated to reflux for 6 hours. The dark mixture was cooled, ammonia in ethanol (2 M, 70 mL) added and the mixture stirred overnight. The solid product was collected by filtration and dried to provide 1.17 g (73%) of the desired product as a yellow solid. MS (DCI/NH<sub>3</sub>) m/z 469/471 (M+H)<sup>+</sup>.

30

Example 3584-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

20

35

Prepared as described for Examples 2-156; using 1-(6-morpholinyl-3-pyridinyl)ethanone as R<sub>1</sub> reagent (for position 7) and N-methylindole-3-carboxaldehyde for R<sub>2</sub> reagent (for 5-position).

MS (DCI/NH<sub>3</sub>) 438 (M+H)<sup>+</sup>;

IR (mic) 3453, 1641, 1556, 1244, 1120 cm<sup>-1</sup>.

40

25

Example 3594-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine

45

A suspension of Example 328 (282 mg, 0.593 mmol) in absolute ethanol (3 mL) was treated sequentially with ethoxyamine hydrochloride (64 mg, 0.65 mmol), and 2 drops

50

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5 conc. aq. HCl, heated to reflux 1.5 hours, cooled and partitioned, between CH<sub>2</sub>Cl<sub>2</sub> (25 mL)  
and saturated NaHCO<sub>3</sub> (15 mL). The separated aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>  
10 (1 x 10 mL), and the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>),  
and concentrated in vacuo. The crude product was purified by flash chromatography  
5 eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to yield 240 mg (78%) of the designated compound.  
<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.19 (t, 3H), 2.41 (m, 2H), 2.58 (m, 2H), 3.77-3.86 (m,  
15 4H), 4.02 (q, 2H), 6.99 (d, 1H), 7.50-7.60 (m, 2H), 7.79 (dt, 1H), 7.85 (m, 2H), 8.47 (dd,  
1H), 8.53 (s, 1H), 9.08 (d, 1H);  
MS (DCI/NH<sub>3</sub>) m/e 518/520 (M+H)<sup>+</sup>;  
10 Anal. calcd for C<sub>23</sub>H<sub>24</sub>BrN<sub>7</sub>O: C, 57.92; H, 4.67; N, 18.91. Found: C, 57.69; H, 4.66; N,  
20 18.65.

#### Example 360

##### 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylcarbomethoxypiperidinyl)-3- pyridinyl)pyrido[2,3-d]pyrimidine

15 Prepared as described for Example 359, substituting carbomethoxyamine for  
ethoxyamine.

30 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.20 (t, 3H), 2.42 (m, 2H), 2.65 (m, 2H), 3.77-3.90 (m,  
4H), 4.13 (q, 2H), 4.61 (s, 2H), 7.01 (d, 1H), 7.55 (m, 2H), 7.79 (dt, 1H), 7.86 (m, 2H),  
20 8.48 (dd, 1H), 8.53 (s, 1H), 9.09 (d, 1H); MS (DCI/NH<sub>3</sub>) m/e 576/578 (M+H)<sup>+</sup>;  
35 Anal. calcd for C<sub>21</sub>H<sub>26</sub>BrN<sub>7</sub>O·0.5 H<sub>2</sub>O: C, 55.39; H, 4.65; N, 16.75. Found: C, 55.66; H,  
4.61; N, 16.37.

#### Example 361

##### 4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3- pyridinyl)pyrido[2,3-d]pyrimidine

40 Example 134 formamide complex (200 mg, 0339 mmol) and 3-amino-1,2-  
propanediol (155 mL, 2.0 mmol) were placed in a 50 mL round-bottomed flask furnished  
45 with a magnetic stirbar. DMSO (dimethyl sulfoxide) (6 mL) was added. The mixture was  
30 then heated to 120 °C for about 10 min until a homogeneous solution was formed.

Catalytic amount of acetic acid was then added, and the reaction mixture was allowed to stir at 120 °C for about 1.5 days. DMSO was removed under vacuum. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and washed with water, NaHCO<sub>3</sub> (saturated), water, and then dried over Na<sub>2</sub>SO<sub>4</sub>. The crude mixture was first purified by column chromatography (SiO<sub>2</sub>), 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The desired product was collected and was subjected to another column chromatographic purification (SiO<sub>2</sub>, ethyl acetate and then 25% NCCH<sub>3</sub>, 7.5% MeOH and 67.5% CH<sub>2</sub>Cl<sub>2</sub>) to give a pure yellow solid (60 mg, 29% yield; M.P. 189-191 °C).  
MS (ESI(+)) = 537/539 (M+H)<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br;  
IR (MIC) ν<sub>max</sub> = 3433, 3354, 2914, 2853, 1568, 1506, 1236, 1114, 945 cm<sup>-1</sup>.

#### Example 362

4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 360, but replacing 3-amino-1,2-propanediol with 4-(3-aminopropyl)morpholine.  
MS (ESI(+)) = 590/592 (M+H)<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br;  
IR (MIC) ν<sub>max</sub> = 3433, 2959, 2854, 1567, 1506, 1235, 1117, 945 cm<sup>-1</sup>.

#### Example 363

4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 360, but replacing 3-amino-1,2-propanediol with histamine.  
MS (ESI(+)) = 557/559 (M+H)<sup>+</sup>; <sup>79</sup>Br/<sup>81</sup>Br;  
IR (MIC) ν<sub>max</sub> = 3433, 3091, 2954, 2893, 2854, 1571, 1564, 1505, 1235, 1123, 944 cm<sup>-1</sup>.

#### Example 364

4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 360, but replacing 3-amino-1,2-propanediol with 3-aminopropionic acid ( $\beta$ -alanine).

MS (ESI(+)) = 53 5/537 (M+H)<sup>+</sup>; <sup>75</sup>Br/<sup>81</sup>Br);

IR (MTC)  $\nu_{\max}$  = 3429, 3051, 2959, 2855, 2528, 1927, 1718, 1585, 1559, 1352, 1332, 1236, 1118, 944 cm<sup>-1</sup>.

#### Example 365

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 328; substituting Example 356 for Example 327.

MS (APCI+) m/z 475 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  8.60(s, 1H), 8.45(d, 1H), 8.28(s, 1H), 7.85 (m, 2H), 7.50 (m, 3H), 4.10 (m, 4H).

#### Example 366

4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359; substituting Example 365 for Example 328 and 4-aminomorpholine for ethoxylamine hydrochloride.

MS (APCI+) m/z 560 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  8.59(s, 1H), 8.40(d, 1H), 8.26(s, 1H), 7.84 (m, 2H), 7.55 (m, 3H), 3.93 (m, 4H), 3.68 (m, 4H), 2.75 (m, 2H), 2.63 (m, 4H), 2.47 (m, 2H)

#### Example 367

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

stepa 4-amino-5-(3-bromo phenyl)-7-(6-chloro-3-pyridazinyl) pyrido[2,3-d]pyrimidine

Prepared by a modification of the method of Example 333 step C, a mixture of 22 mmol of 3-acetyl-6-chloropyridazine (Example 246), 26 mmol of 1-(3-bromophenyl) 1,1-dicyanoethylene, and 110 mmol of ammonium acetate in 150 mL of dichloroethane was

heated at reflux for an hour to give the intermediate amino cyanopyridine, which was purified by flash column chromatography. By a modification of the method of Example 287, the intermediate 2-amino-3-cyano-4-(3-bromo phenyl)-6-((6-chloro) pyridazin-3-yl)pyridine was heated in 40 mL of triethylorthoformate with 1 mmol of ammonium sulfate for one hour. A 2M solution of ammonia in ethanol was added (30 mL) stirring, and after 14 hours, the solid amidine intermediate was collected by filtration and dried in vacuo. The amidine intermediate was then heated in 25 mL of 1,2-dichlorobenzene at 120 °C for two hours. On cooling, a precipitate was deposited. Ether was added, and the precipitate was collected by filtration, washed with ether and dried.

M/z [M+H]<sup>+</sup> C<sub>17</sub>H<sub>10</sub>N<sub>6</sub>BrCl at 413.414, 415.

<sup>1</sup>H NMR (CD<sub>3</sub>CO<sub>2</sub>D) δ 8.72 (d, J = 8.7 Hz, 1 H), 8.64 (s, 1 H), 8.48 (s, 1 H), 7.73 (d, J = 8.7 Hz, 1 H), 7.70 (t, J = 1.0 Hz, 1 H), 7.64 (dt, J = 8.1, 1.0 Hz), 7.45 (dt, J = 8.1, 1.0 Hz, 1 H), 7.42 (m, 1H).

4-amino-5-(3-bromophenyl)-7-(6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

A solution of 0.73 mmol of 4-amino-5-(3'-bromo phenyl)-7-(6-(chloro) pyridazin-3-yl) [2,3-d] pyridopyrimidine (prepared in step a), 3.1 mmol of (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane (Aldrich Chemical Co.), and 2.4 mmol of potassium carbonate was heated at 120 °C in DMSO for 14 hours, then cooled and poured into 10 mL of water. The mixture was partitioned between dichloromethane and water, and the organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to give the title compound. This material was recrystallized from chloroform/methanol and converted to the hydrochloride salt by lyophilization from 12 mL of 2.5 M HCl.

mp 222-226 °C;

CHN calculated for C<sub>22</sub>H<sub>18</sub>N<sub>7</sub>OBr(3.0 HCl): C 45.11, H 3.61, N 16.74; found: C 45.00, H 3.90, N 16.82. MS [M+H]<sup>+</sup> at 478;

IR 3434, 3056, 1640, 1610, 1558, 1376 cm<sup>-1</sup>.

Example 368

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359 substituting Example 365 for Example 328 and methoxylamine hydrochloride for ethoxylamine hydrochloride.

MS (ESI+) m/z 504 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.59(s, 1H), 8.40 (d, 1H), 8.26(s, 1H), 7.82 (m, 2H), 7.54 (m, 3H), 3.90 (m, 4H), 3.77 (s, 1H), 2.62 (m, 2H), 2.47 (m, 2H)

Example 369

4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Sodium and benzyl alcohol were heated at 60 °C in toluene for 3 hours. It was cooled to room temperature and added to a suspension of 4-amino-5-(3-bromo phenyl)-7-(6-chloro-3-pyridazinyl) pyrido[2,3-d]pyrimidine (prepared in Example 367) in anhydrous DMSO to give the title compound. Treatment with 1M HCl ether in chloroform and methanol at room temperature provided the HCl salt.

MS (ESI+) m/z 485 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.07 (bs, 1H), 8.95 (s, 1H), 8.59 (d, 1H), 8.50 (s, 1H), 7.95-7.30 (m, 10H), 5.63 (s, 2H)

Example 370

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Step a 2-amino-3-cyano-4-(3-bromophenyl)-6-(6-chloro-3-pyridyl)pyridine

Prepared as described in Example 244 substituting 5-acetyl-2-chloropyridine for 5-acetyl-1-methylindoline in step c.

25

Step b 4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine

2-Amino-3-cyano-4-(3-bromophenyl)-6-(6-chloro-3-pyridyl)pyridine prepared in step a was reacted with 10 eq. of N,N',N''-methylidynetrisformamide in formamide at 125° for 3 days. The slurry was cooled, poured into 3 volumes of water, and the resulting solid



was collected by filtration and washed with water. The chloropyridyl product was dried under vacuum and used without further purification.

step c 4-methoxypiperidine

4-Hydroxypiperidine is treated with 1 eq. of  $\text{Boc}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  and stirred at room temperature for 5 min. The solution is then washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The protected species is then dissolved in DMF and treated with 7 eq. of NaH. The mixture is stirred for 5 min, then methyl iodide (2 eq) is added, and the reaction is stirred at room temperature overnight. After this time, it is quenched with water and extracted with 2:1 ether-hexanes. The organic solution is dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The oil thus obtained is finally stirred in 4M HCl-dioxane for 30 minutes. The solvent was removed in vacuo, then the residue was basified with 50% aq. NaOH solution and extracted with ether. Drying ( $\text{Na}_2\text{SO}_4$ ) of the extracts, followed by removal of the solvent in vacuo, afforded 4-methoxypiperidine.

Step d.

3.0 equivalents of 4-methoxypiperidine (step c) and 1 equivalent of 4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine (step b) were stirred in DMSO at  $100^\circ$  for 16 hours. The mixture was cooled, quenched with 3 volumes of water, and the precipitated solid was collected by filtration and washed with water. Purification by recrystallization afforded the title compound.  $^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  9.05 (d, 1H), 8.52 (s, 1H), 8.42 (dd, 1H), 7.84 (d, 1H), 7.83 (s, 1H), 7.78 (dt, 1H), 7.54 (2 overlapping m, 2H), 6.99 (br d, 1H), 4.07 (m, 2H), 3.45 (m, 2H), 3.36 (m, 1H), 3.29 (s, 3H), 1.92 (m, 2H), 1.46 (m, 2H); MS (ESI)  $m/z$  491/493 ( $\text{M}^+ + \text{H}$ ,  $^{79}\text{Br}/^{81}\text{Br}$ ).

Example 371

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359; substituting Example 365 for Example 328 and O-tetrahydro-2H-pyran-4-yl-hydroxylamine hydrochloride (JP 94-177353 19940729) for ethoxylamine hydrochloride.

MS (ESI+) m/z 574 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>-d<sub>1</sub>) δ 8.78 (s, 1H), 8.69 (d, 1H), 8.59 (s, 1H), 7.71 (m, 2H), 7.46 (m, 2H), 7.10 (d, 1H), 4.26 (m, 1H), 3.98 (m, 6H), 3.53 (m, 2H), 2.79 (m, 2H), 2.59 (m, 2H), 2.00 (m, 2H), 1.69 (m, 2H)

#### Example 372

4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Sodium isobutoxide was made by heating sodium and isobutanol at 60°C for 45 minutes. 4-amino-5-(3-bromo phenyl)-7-(6-chloro-3-pyridazinyl) pyrido[2,3-d]pyrimidine (prepared as in Example 367) was added to this mixture and heated at 60°C for 2 hours to give the title compound.

MS (APCI+) m/z 451 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.07 (bs, 1H), 8.96 (s, 1H), 8.53 (s, 1H), 8.52 (d, 1H), 7.95 (m, 1H), 7.85 (m, 1H), 7.60 (m, 3H), 4.34 (d, 2H), 2.15 (m, 1H), 1.05 (d, 6H)

#### Example 373

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359; substituting Example 365 for Example 328 and 4-amino-4-N-methylpiperazine for ethoxylamine hydrochloride.

MS (APCI+) m/z 575 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.59 (s, 1H), 8.42 (d, 1H), 8.27 (s, 1H), 7.84 (m, 2H), 7.55 (m, 3H), 3.92 (m, 4H), 2.71 (m, 4H), 2.63 (m, 4H), 2.43 (m, 4H), 2.19 (s, 3H)

#### Example 374

4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 369; substituting tetrahydro-4H-pyran-4-ol for benzyl alcohol.

MS (FAB+) m/z 479 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.80 (bs, 1H), 8.85 (s, 1H), 8.56 (d, 1H), 8.52 (s, 1H), 7.93 (m, 1H), 7.84 (m, 1H), 7.70-7.50 (m, 3H), 5.51 (m, 1H), 3.91 (m, 2H), 3.55 (m, 2H), 2.13 (m, 2H), 1.77 (m, 2H)

#### Example 375

4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 369; substituting N-(2'-hydroxyethyl)-morpholine for benzyl alcohol.

MS (FAB+) m/z 508 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 12.10 (bs, 1H), 10.05 (bs, 1H), 8.92 (s, 1H), 8.57 (d, 1H), 8.48 (s, 1H), 7.95-7.52 (m, 5H), 7.45 (bs, 2H), 5.05 (m, 2H), 3.97 (m, 4H), 3.69 (m, 2H), 3.60-3.18 (m, 4H)

#### Example 376

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Treatment of N-Boc-4-hydroxypiperidine with sodium hydride and ethyl iodide gave N-Boc-4-ethoxypiperidine, which was treated with 4M HCl in dioxane to give 4-ethoxypiperidine.

The title compound was prepared as described for Example 367 substituting 4-ethoxypiperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

MS (FAB+) m/z 506 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.10 (bs, 1H), 8.90 (s, 1H), 8.38 (s, 1H), 8.26 (d, 1H), 7.92-7.42 (m, 5H), 3.78-3.38 (m, 7H), 1.96 (m, 2H), 1.55 (m, 2H), 1.10 (t, 3H)

Example 377

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Treatment of N-Boc-4-hydroxypiperidine with sodium hydride and chloroethyl ethyl ether gave N-Boc-4-(2'-ethoxyl-ethoxyl)-piperidine, which was treated with 4M HCl in dioxane to give 4-(2'-ethoxyl-ethoxyl)-piperidine.

The title compound was prepared as described for Example 367 substituting 4-(2'-ethoxyl-ethoxy)-piperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

MS (APCI+) m/z 550 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.10 (bs, 1H), 8.94 (s, 1H), 8.41 (s, 1H), 8.23 (d, 1H), 7.95-7.45 (m, 5H), 7.39 (bs, 1H), 4.15 (m, 3H), 3.70-3.30 (m, 6H), 1.94 (m, 3H), 1.50 (m, 3H), 1.08 (t, 3H)

Example 378

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

4-(2'-Hydroxyethyl)-piperidine was treated with triethylamine and Boc-anhydride in THF at room temperature. This crude product was treated with mesyl chloride and triethylamine in dichloromethane to give the mesylate. This mesylate was then treated with sodium tetrahydro-4H-pyran-4-oxide (Example 372), followed by deprotection with 4M HCl in dioxane to give 4-(2'-(4''-azacyclohexyl)-ethoxyl)-tetrahydro-4H-pyran.

The title compound was prepared as described for Example 367 substituting 4-(2'-(4''-azacyclohexyl)-ethoxyl)-tetrahydro-4H-pyran for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

MS (APCI+) m/z 590 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.10 (bs, 1H), 8.79 (s, 1H), 8.22 (s, 1H), 8.18 (d, 1H), 7.70-7.40 (m, 5H), 4.42 (m, 2H), 3.63 (m, 2H), 3.34 (m, 3H), 3.19 (m, 2H), 3.01 (m, 2H), 1.70 (m, 5H), 1.33 (m, 2H), 1.23 (m, 2H), 1.08 (m, 2H)

5

Example 379

4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranvloxy)piperidinyl)-3-pyridazinylpyrido[2,3-d]pyrimidine

10

Prepared as described for Example 369; substituting (R)-3-hydroxytetrahydrofuran for benzyl alcohol.

MS (APCI+) m/z 465 (M+H)<sup>+</sup>;

15

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.08 (bs, 1H), 8.93 (s, 1H), 8.52 (d, 1H), 8.51 (s, 1H), 7.98-7.40 (m, 6H), 5.80 (m, 1H), 4.05-3.78 (m, 4H), 2.36 (m, 1H), 2.15 (m, 1H)

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Example 380

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4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranvloxy)piperidinyl)-3-pyridazinylpyrido[2,3-d]pyrimidine

25

Prepared as described for Example 369; substituting (S)-3-hydroxytetrahydrofuran for benzyl alcohol.

MS (APCI+) m/z 465 (M+H)<sup>+</sup>;

15

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.08 (bs, 1H), 8.93 (s, 1H), 8.52 (d, 1H), 8.51 (s, 1H), 7.98-7.40 (m, 6H), 5.80 (m, 1H), 4.05-3.78 (m, 4H), 2.36 (m, 1H), 2.15 (m, 1H)

30

Example 381

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinylpyrido[2,3-d]pyrimidine

35

The title compound was prepared as described for Example 367 substituting anti-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

40

25

MS (APCI+) m/z 508 (M+H)<sup>+</sup>;

45

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.12 (bs, 1H), 8.89 (s, 1H), 8.38 (d, 1H), 8.28 (s, 1H), 7.90-7.40 (m, 5H), 4.40-3.40 (m, 9H), 1.10 (t, 3H)

30

Example 382

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55

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinylpyrido[2,3-d]pyrimidine

Treatment of anti-N-Boc-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) with triphenylphosphine, 4-nitrobenzoic acid and diethyl azodicarboxylate in THF at 0°C to room temperature gave a syn-N-Boc-3-ethoxy-4-(4'-nitrophenylcarbonyloxy)pyrrolidine. This was then hydrolyzed with sodium hydroxide in methanol to give syn-N-Boc-3-ethoxy-4-hydroxypyrrolidine, which was subsequently deprotected with 4M HCl in dioxane to give syn-3-ethoxy-4-hydroxypyrrolidine.

The title compound was prepared as described for Example 367 substituting syn-3-ethoxy-4-hydroxypyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

MS (ESI+) m/z 508 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.17 (bs, 1H), 8.91 (s, 1H), 8.38 (d, 1H), 8.28 (s, 1H),

7.91-7.79 (m, 2H), 7.67-7.49 (m, 4H), 4.80-3.50 (m, 9H), 1.39 (t, 3H)

Example 383

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridylpyrido[2,3-d]pyrimidine

The title compound was prepared as described for Example 370 substituting anti-3-ethoxy-4-hydroxypyrrolidine (Chemical and Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

MS (ESI+) m/z 507 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.00 (bs, 1H), 9.03 (s, 1H), 8.87 (s, 1H), 8.74 (d, 1H),

8.23 (s, 1H), 7.97 (s, 1H), 7.80 (m, 1H), 7.59 (m, 2H), 7.36 (m, 1H), 7.11 (m, 1H), 4.40-3.00 (m, 9H), 1.10 (t, 3H)

Example 384

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinylpyrido[2,3-d]pyrimidine

5 Treatment of anti-N-Boc-3-ethoxy-4-hydroxypyrrolidine (Chemical and  
Pharmaceutical Bulletin, 41, 1993, 132, Okada, T.) with sodium hydride and ethyl iodide  
10 in anhydrous DMF gave anti-N-Boc-3,4-diethoxypyrrolidine, which was subsequently  
deprotected with 4M HCl in dioxane to give anti-3,4-diethoxypyrrolidine.

5 The title compound was prepared as described for Example 367 substituting anti-  
3,4-diethoxypyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by  
15 treatment with 1M HCl ether.

MS (FAB+) m/z 536 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.18 (bs, 1H), 8.82 (s, 1H), 8.39 (d, 1H), 8.34 (s, 1H),  
10 7.90 (m, 2H), 7.70-7.46 (m, 4H), 4.25 (m, 2H), 3.84 (m, 4H), 3.67 (m, 4H), 1.2 (t, 6H)

#### Example 385

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridylpyrido[2,3-  
d]pyrimidine

15 The title compound was prepared as described for Example 370 substituting anti-  
3,4-diethoxypyrrolidine (Example 382) for 4-methoxypiperidine, followed by treatment  
with 1M HCl ether.

MS (ESI+) m/z 535 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.00 (bs, 1H), 9.03 (m, 1H), 8.87 (s, 1H), 8.71 (m, 1H),  
20 8.22 (s, 1H), 7.95 (m, 1H), 7.80 (m, 1H), 7.58 (m, 2H), 7.35 (bs, 1H), 7.09 (m, 1H), 4.25-  
3.20 (m, 10H), 1.12 (t, 6H)

#### Example 386

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridylpyrido[2,3-  
d]pyrimidine

25 Treatment of N-benzyl-3-pyrroline with osmium tetroxide and N-methyl-  
morpholine-N-oxide in THF gave syn-N-Boc-3,4-dihydroxypyrrolidine, which was then  
45 treated with sodium hydride (5eq) and ethyl iodide (5 eq) in DMF to give syn-N-Boc-3,4-  
diethoxypyrrolidine. This was debenzylated under pressure in H<sub>2</sub> atmosphere to afford  
30 syn-3,4-diethoxypyrrolidine.

5

The title compound was prepared as described for Example 370 substituting syn-3,4-diethoxypyrrolidine for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

10

MS (ESI+) m/z 535 (M+H)<sup>+</sup>;

5 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.03 (bs, 1H), 9.03 (m, 1H), 8.89 (s, 1H), 8.74 (m, 1H), 8.25 (s, 1H), 7.95 (m, 1H), 7.62 (m, 1H), 7.60 (m, 2H), 7.39 (bs, 1H), 7.11 (m, 1H), 4.30-3.40 (m, 10H), 1.16 (t, 6H)

15

#### Example 387

10 4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

The title compound was prepared as described for Example 367 substituting syn-3,4-diethoxypyrrolidine (prepared in Example 384) for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 1M HCl ether.

25

15 MS (ESI+) m/z 536.1 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.13 (bs, 1H), 8.87 (s, 1H), 8.35 (d, 1H), 8.28 (s, 1H), 7.82 (m, 2H), 7.63-7.40 (m, 4H), 4.40-3.40 (m, 10H), 1.16 (t, 6H)

30

#### Example 388

20 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

The title compound was prepared as described for Example 370 substituting syn-3-ethoxy-4-hydroxypyrrolidine (prepared as in Example 382) for 4-methoxypiperidine, followed by treatment with 1M HCl ether.

40

25 MS (ESI+) m/z 507 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.00 (bs, 1H), 9.02 (m, 1H), 8.88 (s, 1H), 8.72 (m, 1H), 8.22 (s, 1H), 7.97 (m, 1H), 7.81 (m, 1H), 7.60 (m, 2H), 7.39 (bs, 1H), 7.17 (m, 1H), 4.40-3.40 (m, 9H), 1.17 (t, 3H)

45

30 Example 389

50

55



4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinylpyrido[2,3-d]pyrimidine

Syn-N-benzyl-3-hydroxy-4-(t-butylcarbonylamy)pyrrolidine was made by Sharpless method (JACS 120 1998 1215, Sharpless, K.B.; Tetrahedron asymmetry 5(7) 1994 1333, Saigo K.). This was debenzylated under H<sub>2</sub> to give syn-3-hydroxy-4-(t-butylcarbonylamy)pyrrolidine.

The title compound was prepared as described for Example 367 substituting syn-3-hydroxy-4-(t-butylcarbonylamy)pyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, followed by treatment with 4M HCl dioxane.

MS (ESI+) m/z 479.2 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.07 (bs, 1H), 8.94 (s, 1H), 8.59 (bs, 2H), 8.35 (m, 2H), 7.85 (m, 2H), 7.70-7.30 (m, 4H), 4.70-3.20 (m, 9H)

Example 390 4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridylpyrido[2,3-d]pyrimidine

The title compound was prepared as described for Example 370 substituting syn-3-hydroxy-4-(t-butylcarbonylamy)pyrrolidine (prepared in Example 389) for 4-methoxypiperidine, followed by treatment with 4M HCl dioxane.

MS (APCI+) m/z 478 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.07 (bs, 1H), 9.08 (m, 1H), 8.88 (s, 1H), 8.64 (m, 3H), 8.21 (s, 1H), 7.97 (s, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.36 (m, 1H), 7.03 (m, 1H), 4.65-3.65 (m, 9H)

Example 391

4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 392, except substituting 5-acetyl-2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridine for 5-acetyl-2-morpholinylpyridine, and 3-pyridinecarboxaldehyde for 2,3-dichlorobenzaldehyde. The treatment with HCl/ethanol to form the hydrochloride salt was omitted, and the free base was obtained instead. IR

(MIC) 3500, 3310, 3100, 2982, 1605, 1580, 1555, 1512, 1351, 1238, 1100cm<sup>-1</sup>; MS m/z 442 (M+H)<sup>+</sup>

#### Example 392

5 4-amino-5-(2,3-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine  
4-(2,3-Dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine  
15 (0.47 g) and ammonium sulfate (20 mg) was dissolved in triethylorthoformate (25 ml) and heated to reflux for about 6.5 hours. The reaction mixture was cooled to room temperature, and a 2 M solution of ammonia in ethanol (50 ml) was added. The reaction was stirred at  
20 room temperature for about 18 hours, then heated to reflux for about 6 hours, and then cooled again to room temperature. The solvents were removed under vacuum. The residue was purified by flash chromatography eluting with 5% of 19:1 ethanol:ammonium hydroxide in ethyl acetate, and then converted to the hydrochloride salt by treatment with  
25 HCl/EtOH, followed by removal of solvent and titration with ether to give the title compound.  
15 IR (MIC) 3355, 2980, 1644, 1602, 1437, 1369, 1250cm<sup>-1</sup>;  
MS m/z 453 (M+H)<sup>+</sup>

#### Step a 4-(2,3-dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine

20 Malononitrile (0.33 g) and 2,3-dichlorobenzaldehyde (0.88 g) were dissolved in 1,2-dichloroethane, and 1-2 drops of triethylamine were added. The reaction was stirred at  
35 room temperature for about 2.5 hours, then 5-acetyl-2-morpholinylpyridine (0.62 g) and ammonium acetate (2.31 g) were added. The reaction was heated to reflux for about 5 hours, then cooled to room temperature. The reaction mixture was purified by flash  
40 chromatography eluting with 30% EtOAc/Hexanes.  
25

#### Example 393

#### 4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

45 Prepared according to the procedure of Example 392 except substituting 3-pyridinecarboxaldehyde for 2,3-dichlorobenzaldehyde.  
30

IR (MIC) 3050, 1650, 1603, 1540, 1440, 1375, 1252cm<sup>-1</sup>;  
MS m/z 386 (M+H)<sup>+</sup>

Example 394

4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 392, except substituting 5-acetyl-2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridine for 5-acetyl-2-morpholinylpyridine, and 2-ethoxybenzaldehyde for 2,3-dichlorobenzaldehyde. The treatment with HCl/ethanol to form the hydrochloride salt was omitted, and the free base was obtained instead.

IR (MIC) 3480, 3060, 1738, 1640, 1600, 1560, 1537, 1500, 1345, 1230, 1220, 1100cm<sup>-1</sup>;  
MS m/z 485 (M+H)<sup>+</sup>

Example 395

4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 392, except substituting 2-methoxy-5-bromobenzaldehyde for 2,3-dichlorobenzaldehyde.

IR (MIC) 3440, 2975, 1642, 1600, 1490, 1440, 1370, 1250cm<sup>-1</sup>;  
MS m/z 493 (M+H)<sup>+</sup>

Example 396

4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine  
4-(2,5-dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine

(0.28 g) and ammonium sulfate (10 mg) were dissolved in triethylorthoformate (10 ml) and heated to reflux for about 4 hours. The reaction mixture was cooled to room temperature, and a 2 M solution of ammonia in ethanol (20 ml) was added. The reaction was stirred at room temperature for about 18 hours, then a solution of 1 M sodium methoxide in methanol (5 ml) was added. The reaction was heated to reflux for about 2.5 hours, and then cooled again to room temperature. The reaction mixture was neutralized

with a solution of 1 N aqueous HCl (5 ml) and the solvents were removed under vacuum. The residue was purified by flash chromatography eluting with 2.5% of 19:1 ethanol:ammonium hydroxide in ethyl acetate, and then converted to the hydrochloride salt by treatment with HCl/EtOH, followed by removal of solvent and titration with ether to give the title compound.

IR (MFC) 3480, 3060, 1640, 1600, 1580, 1440, 1371, 1260, 1239 $\text{cm}^{-1}$ ;

MS  $m/z$  453.2 (M+H)<sup>+</sup>

The 4-(2,5-dichlorophenyl)-3-cyano-6-(6-morpholinyl-3-pyridyl)pyridine-2-amine was prepared following the conditions given under Example 392 except substituting 2,5-dichlorobenzaldehyde for 2,3-dichlorobenzaldehyde.

#### Example 397

##### 4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 396, except substituting 2,5-dimethylbenzaldehyde for 2,5-dichlorobenzaldehyde.

IR (MFC) 3420, 2910, 1640, 1600, 1580, 1240 $\text{cm}^{-1}$ ;

MS  $m/z$  413.2 (M+H)<sup>+</sup>

#### Example 399

##### 4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 396, except substituting 3-fluorobenzaldehyde for 2,5-dichlorobenzaldehyde.

IR (KBr) 3480, 1672, 1639, 1617, 1480, 1421, 1315, 1305 $\text{cm}^{-1}$ ;

MS  $m/z$  403 (M+H)<sup>+</sup>

#### Example 400

##### 4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 396, except substituting 3-trifluoromethylbenzaldehyde for 2,5-dichlorobenzaldehyde.

IR (MFC) 3000, 1641, 1600, 1440, 1369, 1324, 1239, 1120 $\text{cm}^{-1}$ ;

MS m/z 453 (M+H)<sup>+</sup>

Example 401

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 327, substituting 3-fluoro-5-trifluoromethylbenzaldehyde for 3-bromobenzaldehyde.

mp: unmelted at 300°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>26</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub>F<sub>4</sub>: 527.1813, found 527.1810.

IR (cm<sup>-1</sup>): 3314, 3081, 1580, 1558, 1515, 1428, 1357, 1329, 1238, 1139, 1106.

Example 402

4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 327, except substituting 3,5-dichlorobenzaldehyde for 3-bromobenzaldehyde.

mp: unmelted at 300°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>23</sub>N<sub>6</sub>O<sub>2</sub>Cl<sub>2</sub>: 509.1254, found: 509.1246

IR (cm<sup>-1</sup>): 3487, 3299, 3065, 1578, 1556, 1515, 1431, 1354, 1238, 1104.

Example 403

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 367, except substituting 1,5-dioxo-9-azaspiro[5.5]undecane for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

mp: δ 190°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>27</sub>H<sub>23</sub>N<sub>7</sub>O<sub>2</sub><sup>81</sup>Br: 536.1233, found: 536.1233.

IR (cm<sup>-1</sup>): 3471, 3297, 3059, 2961, 1579, 1562, 1461, 1407, 1354, 1236, 1104.

Example 404

4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared according to the procedure of Example 327, substituting 4-bromothiophene-2-carboxaldehyde for 3-bromobenzaldehyde.

mp:  $\delta$  245°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>S<sup>79</sup>Br: 525.0703, found: 525.0699.

IR (cm<sup>-1</sup>): 3477, 3296, 3094, 1603, 1579, 1556, 1511, 1428, 1352, 1239, 1104.

Example 405

4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared by the method of Example 367, substituting 4-tertbutylpiperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

mp:  $\delta$  > 270°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>26</sub>H<sub>29</sub>N<sub>7</sub><sup>79</sup>Br: 520.1647, found: 520.1652.

IR (cm<sup>-1</sup>): 3474, 3298, 3085, 2952, 1578, 1553, 1461, 1405, 1351, 1254, 1191, 1159.

Example 406

4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

2-Amino-4-(3-bromophenyl)-3-cyano-6-(6-chloro-3-pyridazinyl)pyridine (310mg), prepared in Example 367, and 1,3-propylenedioxypiperidine (354mg) were dissolved into DMSO (2.5ml) and stirred 48 hours. The reaction mixture was partitioned between 0.4M pH7 aqueous potassium phosphate buffer and worked up as usual. The intermediate was suspended in formamide (15ml) and o-dichlorobenzene (7ml) and heated at 200°C for 2.5h. The reaction mixture was partitioned between salt water and dichloromethane, and the organic phase was separated, filtered through celite, and worked up as usual. Chromatographed (MeOH/EtOAc/CH<sub>2</sub>Cl<sub>2</sub>).

mp:  $\delta$  190°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub><sup>9</sup>Br: 505.1094, found: 505.1095.

IR (cm<sup>-1</sup>): 3472, 3299, 1654, 1578, 1555, 1478, 1418, 1354, 1225.

Example 407

4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared by the method of Example 327, substituting 3-bromothiophene-2-carboxaldehyde for 3-bromobenzaldehyde.

mp: δ 230°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>S<sup>79</sup>Br: 527.0688, found: 527.0692.

IR (cm<sup>-1</sup>): 3472, 3297, 3091, 1611, 1581, 1557, 1519, 1428, 1351, 1334, 1229, 1112.

Example 408

4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

A formamide complex of Example 134 (762mg), Zn(CN)<sub>2</sub> (94mg), and Pd(PPh<sub>3</sub>)<sub>4</sub> (173mg) were heated in DMF (5ml) at 105°C for 3h 40m. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water and worked up as usual. Recrystallization of the crude solid from CHCl<sub>3</sub> gave the title compound.

mp: δ 290°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>20</sub>N<sub>7</sub>O: 410.1724, found: 410.1722.

IR (cm<sup>-1</sup>): 3482, 3313, 2232, 1588, 1542, 1507, 1357, 1240.

Example 409

4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared by the method of Example 367, substituting (S)-O-ethyl-2-hydroxymethylpyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

mp: δ 180°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>28</sub>N<sub>6</sub>O<sub>3</sub><sup>1</sup>Br: 508.1283, found: 508.1285.

IR (cm<sup>-1</sup>) of salt: 3438, 3302, 2974, 1637, 1609, 1588, 1554, 1440, 1374, 1111.

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Step a. (S)-O-ethyl-2-hydroxymethylpyrrolidine

10

A suspension of (S)-N-tertbutyloxycarbonyl-2-hydroxymethylpyrrolidine (1006mg) and crushed NaOH (800mg) in DMSO (20ml) was treated with ethyl iodide (560ml). After the suspension had been stirred for 45m, the reaction mixture was partitioned between 0.2M aq  $\text{KH}_2\text{PO}_4$  and  $\text{Et}_2\text{O}$ , worked up as usual, and concentrated. A solution of the intermediate (1.04g) in MeOH (10ml) was treated with conc aq HCl (1.5ml) and stirred over the weekend. The reaction mixture was concentrated and partitioned between 3M aq  $\text{K}_3\text{PO}_4$  and  $\text{Et}_2\text{O}$ , worked up as usual, and concentrated to give the desired amine

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Example 410

4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

25

Prepared by the method of Example 327, substituting (2S,3S)-2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decane for 4,4-ethylenedioxypiperidine and using 1,2,4-trichlorobenzene as cosolvent with formamide at 200°C in the final cyclization.

15

mp:  $\delta > 235^\circ\text{C}$ ; MS (FAB)<sup>+</sup> m/z calc'd for  $\text{C}_{26}\text{H}_{27}\text{N}_7\text{O}_2$ <sup>+</sup>Br: 550.1389, found: 550.1374.

30

IR ( $\text{cm}^{-1}$ ): 3477, 3046, 2968, 1578, 1559, 1460, 1410, 1353, 1251, 1113.

20 410a. 4,4-(1S,2S-dimethylethanedioxy)piperidine

35

N-tertbutyloxycarbonylpiperidin-4-one (2.59g), (2S,3S)-butanediol (1.464g), and a catalytic amount of p-toluenesulphonic acid were dissolved into benzene (25ml) within a flask fitted with a Dean-Stark trap and condenser, and refluxed 1 day. The reaction mixture was partitioned between aq  $\text{NaHCO}_3$  and ether, and worked up as usual. Chromatographed ( $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ ). This intermediate (3.78g) was dissolved into  $\text{CH}_2\text{Cl}_2$  (10ml) and treated with TFA (3ml). After 90m more TFA (0.5ml) was added, and after another 90min the reaction mixture was concentrated, then conc'd from  $\text{CHCl}_3$ , then from toluene. The intermediate, 6-acetyl-3-chloropyridazine (2.03g), and diisopropylethylamine (9.75ml) were dissolved into methanol (55ml) and heated at 55°C for 2d. The reaction mixture was added to  $\text{Et}_2\text{O}$  and 1M pH7 aq potassium phosphate buffer and worked up as usual. Purified by column chromatography ( $\text{EtOAc}/\text{Hexanes}$ ).

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Example 411

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared by the method of Example 410 (A-312378), substituting cis-1,2-dihydroxycyclopentane for (2S,3S)-butanediol.

15

mp: unmelted at 300°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>27</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub><sup>81</sup>Br: 562.1389, found: 562.1382.

IR (cm<sup>-1</sup>): 3478, 3081, 2959, 1578, 1560, 1460, 1406, 1351, 1246, 1109.

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Example 412

4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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4-Acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl (341mg) was dissolved into CH<sub>2</sub>Cl<sub>2</sub> (0.5ml) and treated with TFA (1ml). After 20m the reaction mixture was concentrated. The intermediate, potassium carbonate (552mg), and 4-amino-5-(3-bromophenyl)-7-(6-chloropyridazin-3-yl)pyrido[2,3-d]pyrimidine (165mg), prepared in Example 367, were suspended in DMSO (2ml) and heated 6h at 120°C. The reaction mixture was partitioned between brine and CH<sub>2</sub>Cl<sub>2</sub> and worked up as usual. Purification by chromatography (CH<sub>3</sub>OH/ CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub>) provided the title compound.

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mp: dec 260°C (sweats and turns deep brown 220°C); MS (FAB)<sup>+</sup> m/z calc'd for C<sub>26</sub>H<sub>26</sub>N<sub>8</sub>O<sub>2</sub><sup>81</sup>Br: 563.1342, found: 563.1329.

IR (cm<sup>-1</sup>): 3487, 3308, 1626, 1578, 1553, 1461, 1416, 1353, 1254, 1073.

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412a.  
N-tertbutyloxycarbonyl-4-oxopiperidine (996mg) and 2-aminoethanol (320ml) were dissolved into ethanol (5ml). After 4h, the reaction mixture was concentrated, and the residue dissolved into CH<sub>2</sub>Cl<sub>2</sub> (8ml) and pyridine (2ml). Acetyl chloride (360ml) was added and the mixture was stirred overnight. More acetyl chloride (350ml) was added then and the same amount 2h later. After 15m more, the reaction mixture was quenched with aq NaHCO<sub>3</sub> and

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worked up as usual but with NaHCO<sub>3</sub> and NaCl in each aqueous wash. This intermediate was purified by chromatography (EtOAc/Hexanes).

#### Example 413

4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure according to Example 412 (A-314908), substituting (2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decane for 412a.

mp:  $\delta$  >130°C; MS (FAB)<sup>+</sup> m/z calc'd for C<sub>28</sub>H<sub>31</sub>N<sub>7</sub>O<sub>4</sub><sup>+</sup>Br: 608.1615, found: 608.1614.

IR (cm<sup>-1</sup>): 3486, 3304, 2928, 1578, 1554, 1461, 1407, 1352, 1235, 1106.

#### Example 414

4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of Example 412 (A-314908), substituting 4,4-(cis-3,4-dioxy-oxacyclopentane)piperidine for 412a.

mp:  $\delta$  280°C; MS (FAB)<sup>+</sup> m/z calc'd for C<sub>28</sub>H<sub>25</sub>N<sub>7</sub>O<sub>3</sub><sup>+</sup>Br: 562.1202, found: 562.1209.

IR (cm<sup>-1</sup>): 3475, 3293, 3094, 1577, 1559, 1461, 1410, 1355, 1229, 1111.

#### Example 415

4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of Example 412 (A-314908), substituting 3-methoxy-1,5-dioxo-9-azaspiro[5.5]undecane for 412a.

mp:  $\delta$  275°C; MS (FAB)<sup>+</sup> m/z calc'd for C<sub>28</sub>H<sub>27</sub>N<sub>7</sub>O<sub>3</sub><sup>+</sup>Br: 564.1359, found: 564.1354.

IR (cm<sup>-1</sup>): 3478, 3293, 3070, 1574, 1564, 1462, 1407, 1349, 1227, 1147, 1101.

#### Example 416

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared following the procedure of Example 412, substituting 1,5-dioxo-3-hydroxymethyl-9-azaspiro[5.5]undecane for 412a. and adding butanol during the work-up.  
mp: unmelted at 300°C (sweats/shrivels >270°C); MS (ESI)<sup>+</sup> m/z: 564/566.  
IR (cm<sup>-1</sup>): 3475, 3302, 1578, 1554, 1462, 1409, 1354, 1237, 1146, 1100.

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Example 417

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4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxo-11-azadispiro[4.2.5.2]pentadecan-11-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

20

Prepared following the procedure of Example 412 (A-314908), substituting 1,7,14-trioxo-11-azadispiro[4.2.5.2]pentadecane for 412a.

mp: unmelted at 300°C; MS (ESI)<sup>+</sup> m/z: 590/592.

IR (cm<sup>-1</sup>): 3476, 3295, 3087, 2968, 1577, 1562, 1465, 1419, 1356, 1149, 1099.

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Example 418

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4-amino-5-(4-tetrahydropyranyl)-7-(4-(4-ethylenedioxy)piperidinyl)pyrido[2,3-d]pyrimidine

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Prepared following the procedure according to Example 327, substituting 1,1-dicyano-3-(4-tetrahydropyranyl)ethene from Example 292 for 3-bromobenzaldehyde, and 6-acetyl-3-chloropyridazine for 5-acetyl-2-chloropyridine at room temperature rather than reflux.

mp: unmelted at 300°C; MS (FAB)<sup>+</sup> m/z calc'd for C<sub>23</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>: 450.2254, found: 450.2266.

IR (cm<sup>-1</sup>): 3544, 3304, 2938, 1579, 1557, 1468, 1415, 1355, 1240, 1104.

35

Example 419

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4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 359; substituting 4-aminomorpholine for ethoxylamine hydrochloride.

MS (DCL/NH<sub>3</sub>) m/z 559 (M+H)<sup>+</sup>;

IR (cm<sup>-1</sup>): 1643, 1602, 1557.

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Example 420

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 419 except substituting 1-amino- 4-N-methylpiperazine for 1-aminomorpholine.

MS (DCI) m/e 572 (M+H<sup>+</sup>);

IR 1647, 1602, 1559.

Example 421

4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 419 except substituting 4-amino- 1,2,4-triazole for 1-aminomorpholine

MS (DCI) m/e 541 (M+H<sup>+</sup>);

IR 1602, 1580.

Example 422

4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared following the procedure of Example 396 except substituting 3-indolylcarboxaldehyde for 2,5-dichlorobenzaldehyde.

MS (DCI), m/z 424.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ. 11.81 (s, 1H), 9.05 (d, 1H), 8.5 (s, 1H), 8.45 (dd, 1H), 7.84 (s, 2H), 7.55 (d, 1H), 7.40 (d, 1H), 7.25 (t, 1H), 7.10 (t, 1H), 6.58 (d, 1H), 3.72 (m, 4H), 3.6 (m, 4H).

Example 423

4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared following the procedure of Example 422 except substituting 5-indolylcarboxaldehyde for 3-indolylcarboxaldehyde, which was prepared according to the procedure of Moyer et. al. Journal of Organic Chemistry, 51, 5106-5110.

1986.

MS (DCI). m/z 452.

IR (mic. cm<sup>-1</sup>) 3448, 1557, 1503, 1234, 943.

Example 424

4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared following the procedures of Example 327 except substituting ethyl 4-piperidinecarboxylate for 4,4-ethlenedioxy piperidine.

MS (DCI) m/e 533 (M+H<sup>+</sup>);

IR (mic. cm<sup>-1</sup>) 1604, 1592, 1560

Example 425

4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-d]pyrimidine

step a 3-acetyl-6-hydroxypyridazine

A solution of 3-acetyl-6-chloropyridazine (prepared in Example 246 step b) (6.0 g, 38.4 mmol) and aq. 3N HCl (70 mmol) in THF (100 mL) was heated at 60°C for 4 h, cooled to ambient temperature, concentrated and chromatographed on silica gel (30% EtOAc-hexane) to obtain the desired compound (3.3 g, 62%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 12.42 (broad s, 1H), 7.98 (d, J=9.0 Hz, 1H), 7.02 (d, J=9.0 Hz, 1H), 2.58 (s, 3H); MS m/z (DCI) 139 (M+H)<sup>+</sup>.

step b 6-acetyl-2-phenylmethyl-3(2H)-pyridazinone

A solution of 3-acetyl-6-hydroxypyridazine (2.9 g, 21.0 mmol), benzyl bromide (2.8 mL, 23.0 mmol) and KOH (1.3 g, 23.0 mmol) in DMF (45 mL) was stirred at ambient temperature for 15 h. The mixture was diluted with EtOAc and washed twice with water. Aqueous layer was extracted with EtOAc and combined organic fractions concentrated and chromatographed (10-25% EtOAc-hexane) to obtain of the desired 6-acetyl-2-phenylmethyl-3(2H)-pyridazinone (3.6 g, 75%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300

MHz)  $\delta$  7.80 (d, J=9.2 Hz, 1H), 7.48-7.27 (m, 5H), 6.90 (d, J=9.2 Hz, 1H), 5.38 (s, 2H), 2.51 (s, 3H); MS m/z (DCI) 229 (M+H)<sup>+</sup>.

The title compound was prepared as described in Example 327 except substituting 6-acetyl-2-phenylmethyl-3(2H)-pyridazinone for 3-acetyl-(4,4-ethylenedioxy-piperidinyl)pyridine  
MS (DCI) m/e 485 (M+H)<sup>+</sup>;  
IR 1640, 1618, 1560.

#### Example 426

4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared following the procedure of Example 424 except substituting 3-acetyl-6-(4-N-morpholinylcarboxamide)piperidinylpyridine for ethyl-4-piperidinecarboxylate derivative.

MS (ESI<sup>+</sup>), m/z 575 (M+H)<sup>+</sup>;  
IR (MFC); cm<sup>-1</sup>, 3486, 1557, 1211, 933.

3-acetyl-6-(4-N-morpholinylcarboxamide)piperidinylpyridine:

2-chloro-5-acetylpyridine (6g) and ethyl isonipecotatate (6.1g) was refluxed in ethanol. The volatiles were evaporated to leave 2-(1'-ethyl isonipecotatate)-4-acetylpyridine. This material was treated with aqueous lithium hydroxide, followed by acidification and filtration. The resulting acid (1.5 g) was treated with morpholine (2.4 g), hydroxybenzotriazole (1.3g) and 1-(3-Dimethylaminopropyl)-3-carbodiimide, to afford the desired compound.

MS (DCI) m/z. 318 (M+H)<sup>+</sup>.

#### Example 427

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of Example 426 except substituting 4-aminomorpholine for morpholine.

MS (ESI) m/z 589 (M+H)<sup>+</sup>;

IR (cm<sup>-1</sup>) 3490, 1557, 1351, 1111.

#### Example 428

4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of Example 426 except substituting dimethylamine for morpholine.

MS (ESI) m/z 532 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz; DMSO-d<sub>6</sub>) 8.9.05 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.85 (s, 2H), 7.78 (dt, 1H), 7.55 (s, 1H), 6.99 (d, 1H), 4.49 (d, 2H), 3.09 (s, 2H), 3.00 (m, 3H), 2.80 (s, 3H), 1.7 (m, 2H), 1.54 (m, 2H).

#### Example 429

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of Example 426 except substituting N-methyl-N-methoxyethylamine for morpholine.

MS (ESI<sup>+</sup>) m/z 576, (M+H)<sup>+</sup>;

IR (mic, cm<sup>-1</sup>) 3489, 1555, 1118, 936.

#### Example 430

4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure of 392, substituting 4-quinolinecarboxaldehyde for 2,3-dichlorobenzaldehyde.

MS (ESI<sup>+</sup>). m/z 436 (M+H)<sup>+</sup>;

IR (mic., cm<sup>-1</sup>) 3488, 1580, 1557, 1227, 936.

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Example 431

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

5 Prepared following the procedure of Example 426, except substituting N-methoxyethylamine for morpholine...

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MS (ESI+) M/z 564, (M+H)<sup>+</sup>;  
IR (cm<sup>-1</sup>) 3310, 1560, 1210, 954.

10

Example 432

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 370 except substituting 4-hydroxypiperidinylpiperidine for 4-methoxypiperidine, which was prepared as follows:  
ethyl isonipecotatate (10g) was treated with lithium aluminum hydride (2.53g) in tetrahydrofuran for 36 hours.

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MS. (ESI+) m/z 491 (M+H)<sup>+</sup>.

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Example 433

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4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 370 except substituting 1,4-dioxo-8-azaspiro[4.5]decane for 4-methoxypiperidine and substituting the dicyanostyrene derived from 2-bromobenzaldehyde instead of the 3-bromoderivative.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.05 (d, 1H), 8.53 (s, 1H), 8.44 (dd, 1H), 7.91 (d, 1H), 7.83 (s, 1H), 7.66 (d, 2H), 7.56 (m, 1H), 7.04 (d, 1H), 3.93 (s, 3H), 3.77 (m, 4H), 1.67 (m, 4H);

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MS (ESI) m/z 519/521 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 434

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 433 except substituting 4-hydroxypiperidine for 4,4-ethylenedioxy-piperidine. IR (KBr pellet)  $\nu_{\max}$  3485, 3298, 3198, 2938, 2848, 1600, 1574, 1557, 1357, 1225, 1024, 766  $\text{cm}^{-1}$ ; MS (ESI)  $m/z$  477/479 ( $M^+ + H$ ,  $^{79}\text{Br}/^{81}\text{Br}$ ).

Example 435

4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetyl-piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 1-acetyl-piperazine for 4-methoxypiperidine.

$^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  9.09 (d, 1H), 8.53 (s, 1H), 8.48 (dd, 1H), 7.86 (s, 1H), 7.85 (s, 1H), 7.78 (dt, 1H), 7.54 (m, 2H), 7.00 (d, 1H), 3.63-3.73 (m, 4H), 3.55-3.59 (m, 4H), 2.06 (s, 3H); MS (ESI)  $m/z$  504/506 ( $M^+ + H$ ,  $^{79}\text{Br}/^{81}\text{Br}$ ).

Example 436

4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-cyanopiperidine for 4-methoxypiperidine, which was prepared as follows: isonipecotamide was heated in  $\text{POCl}_3$  at reflux for 2 hours and then was cooled to rt. Most of the  $\text{POCl}_3$  was removed in vacuo, and the remaining syrup was carefully quenched with ice. The melted aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvent in vacuo afforded 4-cyanopiperidine as a grey-white semi-solid.

$^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  9.07 (d, 1H), 8.53 (s, 1H), 8.45 (dd, 1H), 7.85 (m, 2H), 7.76-7.80 (m, 1H), 7.52 (m, 2H), 7.02 (d, 1H), 3.95-4.02 (m, 2H), 3.46-3.55 (m, 2H), 3.17 (m, 1H), 1.94-1.99 (m, 2H), 1.74-1.80 (m, 2H); MS (ESI)  $m/z$  486/488 ( $M^+ + H$ ,  $^{79}\text{Br}/^{81}\text{Br}$ ).

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Example 437

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

5

Prepared as described for Example 370 except substituting 1-(4-fluorophenyl)piperazine for 4-methoxypiperidine.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.10 (d, 1H), 8.53 (s, 1H), 8.48 (dd, 1H), 7.85 (m, 2H), 7.78 (dt, 1H), 7.55 (m, 2H), 7.00-7.11 (m, 5H), 3.81 (m, 4H), 3.21 (m, 4H);  
MS (ESI) m/z 556/558 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 438

4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 370 except substituting morpholine for 4-methoxypiperidine and substituting the dicyanostyrene derived from 4-fluorobenzaldehyde instead of the 3-bromoderivative.

15

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.08 (d, 1H), 8.53 (s, 1H), 8.47 (dd, 1H), 7.83 (s, 1H), 7.65 (m, 2H), 7.44 (m, 2H), 6.99 (d, 1H), 3.59-3.73 (m, 8H);  
MS (ESI) m/z 403 (M<sup>+</sup>+H).

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Example 440

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4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine

Step a 3-acetyl-6-morpholinylbenzenesulphonamide

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A solution of 4-acetylbenzenesulfonyl chloride in CH<sub>2</sub>Cl<sub>2</sub> at -78° is treated with 2 equivalents of morpholine. The mixture is stirred at -78° for 1 hour and then warmed to rt and stirred for 2 additional hours. After this time, the mixture is diluted with EtOAc and is washed with water and brine. The solution is dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to afford the desired 3-acetyl-6-morpholinylbenzenesulphonamide.

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Step b 2-amino-3-cyano-4-(3-bromophenyl)-6-(6-morpholinylbenzenesulphonamide)pyridine

3-acetyl-6-morpholinylbenzenesulphonamide is then cyclized as described in example 244, using dicyanostyrene derived from 3-bromobenzaldehyde, to the desired 2-amino-3-cyano-4-(3-bromophenyl)-6-(6-morpholinylbenzenesulphonamide)pyridine

The material prepared in step b is converted to the title compound by cyclization with trisformamide using conditions described in Example 370.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.62 (s, 1H), 8.60 (d, 2H), 8.05 (s, 1H), 7.89-7.92 (m, 3H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 3.65 (m, 4H), 2.94 (m, 4H);

MS (ESI) m/z 526/528 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 441

4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulphonamide)pyrido[2.3-d]pyrimidine

Prepared as described for Example 440 except substituting 1,4-dioxo-8-azaspiro[4.5]decane for morpholine in step a.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.62 (s, 1H), 8.58 (d, 2H), 8.05 (s, 1H), 7.91-7.93 (m, 3H), 7.80 (dt, 1H), 7.53-7.63 (m, 2H), 3.80 (s, 4H), 3.06 (m, 4H), 1.69 (m, 4H);  
MS (ESI) m/z 582/584 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 442

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulphonamide)pyrido[2.3-d]pyrimidine

Prepared as described for Example 440 except substituting n-cyclopropylamine for morpholine in step a.

IR (KBr pellet) ν<sub>max</sub> 3478, 3301, 3059, 2847, 2761, 2664, 1730, 1696, 1642, 1579, 1567, 1486, 1349, 1327, 1156, 1094, 887, 844, 828, 798 cm<sup>-1</sup>;  
MS (ESI) 496/498 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 443

4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine

Prepared as described for Example 440 except substituting piperidine for morpholine in step a

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.61 (s, 1H), 8.57 (d, 2H), 8.02 (s, 1H), 7.88-7.90 (m, 3H), 7.80 (dt, 1H), 7.53-7.62 (m, 2H), 2.95 (m, 4H), 1.56 (m, 4H), 1.38 (m, 2H); MS (ESI) 524/526 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

Example 444

4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine

Prepared as described for Example 440 except substituting 4-cyanopiperidine (prepared in Ex. 436) for morpholine in step a.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.62 (s, 1H), 8.60 (d, 2H), 8.05 (s, 1H), 7.93 (s, 1H), 7.90 (m, 2H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 3.24 (m, 2H), 2.94 (m, 1H), 2.80 (m, 2H), 1.95 (m, 2H), 1.77 (m, 2H); MS (ESI) 549/551 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

Example 445

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine

Prepared as described for Example 440 except substituting cyclopropylmethylamine for morpholine in step a.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.61 (s, 1H), 8.52 (d, 2H), 8.01 (d, 1H), 7.96 (d, 2H), 7.79-7.90 (m, 3H), 7.56 (m, 2H), 2.73 (m, 2H), 0.81 (m, 1H), 0.34 (m, 2H), 0.09 (m, 2H); MS (ESI) m/z 510/512 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

Example 446

4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzenesulfonamide)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 440 except substituting dimethylamine for morpholine in step a.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.62 (s, 1H), 8.59 (d, 2H), 8.04 (s, 1H), 7.90-7.93 (m, 3H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 2.67 (s, 6H);

5 MS (ESI) m/z 484/486 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 447

4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-

hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine

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10 Prepared as described for Example 440 except substituting (S-(+)-2-

hydroxymethylpyrrolidine for morpholine in step a.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.61 (s, 1H), 8.56 (d, 2H), 8.03 (s, 1H), 7.99 (d, 2H), 7.90 (m, 1H), 7.81 (dt, 1H), 7.53-7.62 (m, 2H), 4.87 (t, 1H), 3.57 (m, 2H), 3.12 (m, 2H), 1.79 (m, 2H), 1.44 (m, 2H);

15 MS (ESI) m/z 540/542 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 448

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine

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20 Prepared as described for Example 440 except substituting 4-hydroxypiperidine for morpholine in step a.

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 8.62 (s, 1H), 8.59 (d, 2H), 8.04 (s, 1H), 7.90-7.94 (m, 3H), 7.81 (dt, 1H), 7.52-7.63 (m, 2H), 4.86 (m, 1H), 3.06 (m, 4H), 1.91 (m, 2H), 1.69 (m, 2H);  
MS (ESI) m/z 540/542 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 449

4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-

45

dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine

Prepared as described for Example 440 except substituting cis-2,6-

30 dimethylmorpholine for morpholine in step a.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.62 (s, 1H), 8.59 (d, 2H), 8.04 (s, 1H), 7.90 (m, 3 H), 7.80 (dt, 1H), 7.52-7.61 (m, 2H), 3.53-3.66 (m, 4H), 1.89 (m, 2H), 1.05 (d, 6H); MS (ESI) m/z 554/556 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 450

##### 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 using steps a and b except substituting 3-fluoro-4-thiomorpholinylacetophenone for 5-acetyl-2-chloropyridine in step a which was prepared as follows 3',4'-difluoroacetophenone and thiomorpholine are stirred in DMSO at 100° for 12 hours. The mixture is cooled and quenched with water. The resulting beige solid, 3'-fluoro-4'-thiomorpholino-acetophenone, was collected by filtration and washed with water.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.55 (s, 1H), 8.11 (m, 1H), 7.91 (s, 1H), 7.86 (m, 1H), 7.78 (dt, 1H), 7.55 (m, 2H), 7.19 (t, 1H), 3.41 (m, 4H), 2.77 (m, 4H); MS (ESI) m/z 496/498 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 451

##### 4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described in Example 370 except substituting thiomorpholine for 4-methoxypiperidine component and dicyanostyrene derived from 4-fluorobenzaldehyde for the 3-bromo derivative.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.06 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.82 (s, 1H), 7.64 (m, 2H), 7.44 (m, 2H), 7.01 (d, 1H), 4.03 (m, 4H), 2.65 (m, 4H); MS (ESI) m/z 419 (M<sup>+</sup>+H).

#### Example 452

##### 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared by substituting Example 451 for Example 331 as described in Example 332.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.10 (d, 1H), 8.53 (s, 1H), 8.51 (dd, 1H), 7.85 (s, 1H), 7.65 (m, 2H), 7.44 (m, 2H), 7.18 (d, 1H), 4.18 (m, 4H), 3.18 (m, 4H);

MS (ESI) m/z 451 (M<sup>+</sup>+H).

#### Example 453

4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Step a 4-hydroxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

Example 134 was dissolved in 10:1 acetic acid : water. The mixture was heated to reflux for 1 day and cooled. The desired product was collected by filtration.

The 4-hydroxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine was treated with K<sub>2</sub>CO<sub>3</sub> (5 eq) and 18-crown-6 (7 eq) in DMF at rt. After 1 hour, methyl iodide (30 eq) added, and the reaction continued to stir at rt. After 3 hours, the reaction was quenched with water, and the resulting solid was collected by filtration and purified by chromatography to afford the title compound.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.07 (d, 1H), 8.60 (s, 1H), 8.45 (dd, 1H), 7.83 (s, 1H), 7.60 (m, 2H), 7.39 (m, 2H), 6.98 (d, 1H), 3.61-3.73 (m, 8H), 3.38 (s, 3H);

MS (ESI) m/z 478/480 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 454

4-amino-5-(3-bromophenyl)-7-(4-(4-dioxo-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

step a 4-acetylbenzoylchloride

4-Acetylbenzoic acid is stirred with thionyl chloride at reflux for 90 min. The solution is cooled to roomtemperature, and the thionyl chloride is removed under reduced pressure. Residual SOCl<sub>2</sub> is removed by evaporation with CH<sub>2</sub>Cl<sub>2</sub>, and the remaining yellow residue is used without further purification.

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Step b 4-(4',4'-ethylenedioxy)piperidinyl)acetophenone

4-acetylbenzoylchloride prepared in step a is dissolved in CH<sub>2</sub>Cl<sub>2</sub> and treated with 3 eq. of 4,4-ethylenedioxy piperidine. The reaction mixture is stirred overnight at rt and is then washed with water and brine. The solution is dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to afford the desired amide.

Step c

Example 454 was prepared as described for steps a and b of Example 370, substituting the 4-(4',4'-ethylenedioxy piperidinyl)acetophenone prepared above for the 5-acetyl-2-chloropyridine in step a. Substituting the 4-(4',4'-ethylenedioxy piperidinyl)acetophenone prepared in step b for the 5 acetyl.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.59 (s, 1H), 8.39 (d, 2H), 7.97 (s, 1H), 7.89 (m, 1H), 7.80 (dt, 1H), 7.52-7.60 (m, 4H), 3.92 (s, 4H), 3.70 (m, 2H), 3.40 (m, 2H), 1.68 (m, 4H); MS (ESI) m/z 548/548 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

Example 455

4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 454 except substituting cyclopropyl amine for 4,4-ethylenedioxy piperidine.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.60-8.62 (m, 2H), 8.42 (d, 2H), 7.99 (d, 1H), 7.98 (d, 1H), 7.52-7.62 (m, 2H), 2.89 (m, 1H), 0.67-0.75 (m, 2H), 0.58-0.63 (m, 2H); MS (ESI) m/z 460/462 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

Example 456

4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 454 except substituting morpholine for 4,4-ethylenedioxy piperidine.



<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.74 (s, 1H), 8.41 (d, 2H), 7.98 (s, 1H), 7.89 (m, 1H), 7.80 (dt, 1H), 7.52-7.61 (m, 4H), 3.52-3.71 (m, 8H);  
MS (ESI) m/z 490/492 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 457

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting cyclopropyl amine for 4-hydroxypiperidine.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.99 (d, 1H), 8.52 (s, 1H), 8.40 (dd, 1H), 7.83 (m, 1H), 7.76-7.80 (m, 2H), 7.51-7.58 (m, 2H), 7.40 (d, 1H), 6.73 (d, 1H), 2.62 (m, 1H), 0.76 (m, 2H), 0.48 (m, 2H);  
MS (ESI) m/z 433/435 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 458

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 454 except substituting 4-hydroxypiperidine for 4,4-ethylenedioxypiperidine.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.59 (s, 1H), 8.40 (d, 2H), 8.25 (s, 1H), 7.97 (s, 1H), 7.89 (t, 1H), 7.79 (dt, 1H), 7.56 (m, 3H), 5.06 (m, 1H), 3.96 (m, 2H), 3.48 (m, 2H), 1.93 (m, 2H), 1.64 (m, 2H);  
MS (ESI) m/z 504/506 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 459

4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting (S)-(+)-2-hydroxymethylpyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.58 (s, 1H), 8.38 (d, 1H), 8.26 (s, 1H), 7.84 (m, 1H), 7.81 (dt, 1H), 7.57 (2 overlapping m, 2H), 7.16 (br d, 1H), 4.91 (t, 1H), 3.63 (m, 2H), 3.44 (m, 2H), 2.05 (m, 4H);  
MS (ESI) m/z 478/480 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 4604-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-(2-ethoxyethoxy)piperidine for 4-methoxypiperidine, which was prepared as follows. 4-Hydroxypiperidine is treated with 1 eq. of Boc<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> and stirred at rt for 5 min. The solution is then washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The protected species is then dissolved in DMF and treated with 7 eq. of NaH. The mixture is stirred for 5 min, then 2-ethoxy-1-chloroethane (2 eq) is added, and the reaction is stirred at rt overnight. After this time, it is quenched with water and extracted with 2:1 ether-hexanes. The organic solution is dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The oil thus obtained is finally stirred in 4M HCl-dioxane for 30 minutes. The solvent was removed in vacuo, then the residue was basified with 50% aq. NaOH solution and extracted with ether. Drying (Na<sub>2</sub>SO<sub>4</sub>) of the extracts, followed by removal of the solvent in vacuo, afforded the desired 4-alkoxy-piperidine.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.43 (dd, 1H), 7.85 (m, 2H), 7.78 (dt, 1H), 7.53 (m, 2H), 6.99 (d, 1H), 4.07 (m, 2H), 3.56 (m, 2H), 3.48 (m, 2H), 3.45 (q, 2H), 3.29 (m, 2H), 3.27 (m, 1H), 1.92 (m, 2H), 1.45 (m, 2H), 1.10 (t, 3H);  
MS (ESI) m/z 549/551 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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Example 4614-amino-5-(3-bromophenyl)-7-(6-hexahydroprymidine)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 370 except substituting hexahydropyrimidine for 4-methoxypiperidine, which was prepared according to Shustov, et al Tetrahedron 1985. 41. 5719.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.23 (d, 1H), 8.89 (s, 1H), 8.58 (dd, 1H), 8.21 (s, 1H), 7.95 (m, 1H), 7.83 (m, 1H), 7.61 (m, 2H), 7.29 (d, 1H), 5.13 (m, 1H), 3.91 (m, 2H), 3.69 (m, 2H), 3.32 (m, 2H), 1.83 (m, 2H); MS (ESI) m/z 462/464 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

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#### Example 462

4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 370 except substituting 4,4-difluorocyclohexylcarboxaldehyde for 3-bromobenzaldehyde and 4,4-ethylenedioxypiperidine for 4-methoxypiperidine. The 4,4-difluorocyclohexylcarboxaldehyde was prepared as follows: 4-Oxo-cyclohexanecarboxylic acid ethyl ester was stirred with 10 eq of (diethylamino)sulfur trifluoride in benzene at rt for 24 hours. The mixture was diluted with ether and was quenched carefully with saturated NaHCO<sub>3</sub> solution. The organic solution was separated, washed with brine, and concentrated in vacuo to afford 4,4-difluoro-cyclohexanecarboxylic acid ethyl ester. This material was treated with 1 eq. of DIBAL-H in dry ether at -78° to afford, after workup, 4,4-difluoro-cyclohexanecarboxaldehyde.

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<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.13 (d, 1H), 8.79 (s, 1H), 8.44 (dd, 1H), 8.06 (s, 1H), 7.10 (d, 1H), 3.94 (s, 4H), 3.82 (m, 4H), 1.70 (m, 4H); MS (ESI) m/z 483 (M<sup>+</sup>+H).

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#### Example 463

4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 370 except substituting (S??)-2-ethoxyethoxypyrrolidine for 4-methoxypiperidine. (R)-2-ethoxyethoxypyrrolidinyl was prepared as follows:

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(R)-(+)-3-Pyrrolidinol is treated with 1 eq. of  $\text{Boc}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  and stirred at rt for 5 min. The solution is then washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The protected species is then dissolved in DMF and treated with 7 eq. of NaI. The mixture is stirred for 5 min, then 2-ethoxy-1-chloroethane (2 eq) is added, and the reaction is stirred at rt overnight. After this time, it is quenched with water and extracted with 2:1 ether-hexanes. The organic solution is dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The oil thus obtained is finally stirred in 4M HCl-dioxane for 30 minutes. The solvent was removed in vacuo, then the residue was basified with 50% aq. NaOH solution and extracted with ether. Drying ( $\text{Na}_2\text{SO}_4$ ) of the extracts, followed by removal of the solvent in vacuo, afforded the 3-alkoxy-pyrrolidine derivative.

$^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  9.06 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.84 (m, 2H), 7.79 (dt, 1H), 7.56 (2 overlapping m, 2H), 6.62 (br d, 1H), 4.24 (m, 1H), 3.58 (m, 4H), 3.48 (m, 4H), 3.42 (q, 2H), 2.10 (m, 2H), 1.09 (t, 3H); MS (ESI)  $m/z$  535/537 ( $\text{M}^+ + \text{H}$ ,  $^{79}\text{Br}/^{81}\text{Br}$ ).

#### Example 464

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Was prepared from Example 603 by treatment with 0.1 eq.  $\text{OsO}_4$  and 1.2 eq. NMO in 10%  $\text{MeOH}-\text{CH}_2\text{Cl}_2$  and the mixture was refluxed for 13 hours and was then quenched with water and filtered. The solid thus obtained was purified by recrystallization to afford the title compound.

$^1\text{H}$  NMR (300 MHz,  $d_6$ -DMSO)  $\delta$  9.05 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.85-7.77 (m, 3H), 7.58-7.5 (m, 2H), 6.58 (d, 1H), 5.0 (d, 2H), 4.17 (m, 2H), 3.6 (m, 2H).

MS  $m/z$  480 ( $\text{M} + \text{H}$ )<sup>+</sup>

#### Example 465

4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Example 464 was stirred with 5 eq. of carbonyl diimidazole and 12 eq. of imidazole in DMSO at 100° for 12 hours. The solution was then cooled, quenched with water, and the resulting solid was collected by filtration and washed with water.

Purification by chromatography afforded the title compound.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.10 (d, 1H), 8.54 (s, 1H), 8.51 (dd, 1H), 7.87 (m, 2H), 7.78 (dt, 1H), 7.54 (m, 2H), 6.91 (d, 1H), 5.48 (m, 2H), 4.18 (d, 2H), 3.48 (m, 2H); MS (ESI) m/z 505/507 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 466

4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting pyrroline for 4-methoxypiperidine and subsequent oxidation of this material by the following procedure: treatment with 0.1 eq. OsO<sub>4</sub> and 1.2 eq. NMO in 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub> containing a few drops of glacial acetic acid. The mixture was refluxed for 13 hours and was then quenched with water and filtered. The solid thus obtained was purified by recrystallization to afford the title compound.

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.93 (s, 1H), 8.47 (s, 1H), 8.31 (d, 1H), 7.92 (t, 1H), 7.83 (dt, 1H), 7.59 (m, 2H), 7.20 (d, 1H), 4.23 (m, 2H), 3.55 (m, 4H); MS (ESI) m/z 480/482 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 467

4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting (S,R)-2-hydroxymethyl-4-hydroxypyrrolidine for 4-methoxypiperidine, which was prepared as follows: N-Boc-hydroxyproline was treated with BH<sub>3</sub>-SMC<sub>2</sub> (4 eq) in ether at roomtemperature. After 16 hours, the reaction was quenched with water and K<sub>2</sub>CO<sub>3</sub> and was extracted with EtOAc. The combined extracts were dried and concentrated in vacuo to afford N-Boc-hydroxyprolinol. The Boc group was then removed (HCl-dioxane, rt).

<sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.42 (dd, 1H), 7.82 (m, 2H), 7.78 (dt, 1H), 7.54 (m, 2H), 6.66 (d, 1H), 5.02 (d, 1H), 4.95 (t, 1H), 4.47 (m, 1H), 4.23 (m, 1H), 3.46-3.66 (m, 4H), 2.16 (m, 1H), 1.96 (m, 1H); MS (ESI) m/z 493/495 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 468

##### 4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting R-2-hydroxymethylpyrrolidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.58 (s, 1H), 8.38 (d, 1H), 8.26 (s, 1H), 7.84 (m, 1H), 7.80 (dt, 1H), 7.56 (2 overlapping m, 2H), 7.16 (d, 1H), 4.89 (t, 1H), 4.23 (br, 1H), 3.62 (m, 2H), 3.45 (m, 2H), 2.05 (m, 4H); MS (ESI) m/z 478/480 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 469

##### 4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane for 4-methoxypiperidine, which was prepared according to Portoghese, et al J. Med. Chem 1971, 14, 288. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 9.05 (d, 1H), 8.52 (s, 1H), 8.43 (dd, 1H), 7.82 (m, 2H), 7.78 (dt, 1H), 7.57 (m, 2H), 6.67 (m, 1H), 5.01 (s, 1H), 4.71 (s, 1H), 3.82 (dd, 1H), 3.68 (d, 1H), 3.54 (dd, 1H), 3.38 (d, 1H), 1.93 (m, 2H); MS (ESI) m/z 475/477 (M<sup>+</sup>+H, <sup>79</sup>Br/<sup>81</sup>Br).

#### Example 470

##### 4-amino-5-(3-bromophenyl)-7-(6-(2-imidazolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 1,2-ethanediamine for 4-methoxypiperidine and the resulting crude product was stirred in DMSO with carbonyl

diimidazole (4.7 eq) and imidazole (9 eq) at 100° for 16 hours. Solution quenched with water, then the solvent was removed by lyophilization. Chromatography of the residue afforded the title compound.

IR (KBr pellet)  $\nu_{\max}$  3363, 3201, 3122, 3049, 2941, 1734, 1645, 1611, 1566, 1484, 1381,

1270, 1162, 1058, 808, 781, 767  $\text{cm}^{-1}$ ;

MS (ESI) 462/464 ( $\text{M}^+ + \text{H}$ ,  $^{79}\text{Br}/^{81}\text{Br}$ ).

#### Example 472

##### 4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

A mixture of 7.6 mmol of 2,2-dimethyl-4-pentenal (Aldrich Chemical Co.), 24.4 mmol of 1-morpholino-5-acetylpyridine, 7.6 mmol of malononitrile, and 29 mmol of ammonium acetate in ethylene dichloride was heated at 120 °C in a sealed tube for 16 hours. The reaction was cooled, poured into dichloromethane, and washed with water. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , concentrated in vacuo, and purified by flash chromatography, eluting with ethyl acetate/dichloromethane to give the intermediate product pyridine.

A mixture of 1.7 mmol of this intermediate pyridine, and 45 mg of ammonium sulfate was heated in 10 mL of triethyl orthoformate at 140 °C in a sealed tube for one hour. After cooling, the reaction was poured into 40 mL of 2-M ammonia in ethanol with stirring. After 24 hours, 300 mL of hexane was added, and the solid collected by filtration to give the intermediate amidine. A mixture of 0.87 mmol of this intermediate amidine and 3 mmol of potassium t-butoxide in 10 mL of dioxane was heated at 135 °C in a sealed tube for 16 hours. After cooling, the reaction was poured into dichloromethane, washed with water, and dried over sodium sulfate. The residue was purified by flash chromatography, eluting with methanol/dichloromethane, to give the title compound as a yellow glass.

CHN analysis calculated for  $\text{C}_{27}\text{H}_{26}\text{N}_6\text{O}$ (0.5 Methanol) C 66.48, H 6.94, N 20.67; found: C 66.18, H 6.83, N 20.65.

MS (FAB) calc. for  $\text{C}_{27}\text{H}_{27}\text{N}_6\text{O}$ : 391.2246; found: 391.2238.

IR 3417, 3340, 2965, 2853, 1603, 1584, 1563, 1533, 1241  $\text{cm}^{-1}$ .

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Example 473

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4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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5 A solution of 4-aminoacetophenone and triethylamine in toluene at -78 C was treated with phosgene, warmed to ambient temperature and concentrated under reduced pressure to give 4-isocyanateacetophenone. This product was reacted with ethyl 2-aminobenzoate in refluxing THF for 16 hours, cooled and treated with 1M potassium tert-butoxide to give after silica gel purification 3-(4-acetylphenyl)-2,4(1H,3H)-quinazolin-6-one. Using the procedure in Example 244c except substituting 2,4(1H,3H)-quinazolin-6-one for N-methyl-5-acetylmorpholine gave the title compound.

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MS (APCI +) m/z 537 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.59 (s, 1H), 8.35 (m, 2H), 7.97 (s, 1H), 7.91 (t, 1H), 7.78 (m, 1H), 7.71 (dd, 1H), 7.63 (m, 1H), 7.55 (t, 1H), 7.35-7.24 (m, 3H), 6.92 (d, 1H), 6.72 (dt, 1H).

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Example 474

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4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described in Example 473 except substituting ammonia for morpholine.

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MS (APCI +) m/z 422 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.87 (d, 1H), 8.66 (s, 1H), 8.62 (bs, 1H), 8.44 (d, 1H), 8.42 (s, 1H), 8.07 (bs, 1H), 7.88 (m, 1H), 7.83 (m, 1H), 7.63 (m, 1H), 7.58 (t, 1H).

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Example 475

4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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A solution of 3-chloro-6-pyridazinoyl chloride (Mourad et al.; J. Heterocycl. Chem., 29 6. (1992), pp1583-1592) and triethylamine in dichloroethane was treated with morpholine to give 3-chloro-6-morpholinocarbonyl pyridazine. This intermediate was

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then treated with tributyl ethoxyvinyl tin under Stille conditions to give 3-acetyl-6-morpholinocarboxamide pyridazine. Treatment of this intermediate as in Example 246 replacing 3-acetyl-6-dimethylaminopyridazine gave the title compound.

MS (APCI +) m/z 492 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.84 (d, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 8.17 (d, 1H), 7.89 (t, 1H), 7.84 (m, 1H), 7.65 (m, 1H), 7.57 (t, 1H), 3.74 (s, 4H), 3.61 (m, 2H), 3.51 (m, 2H).

#### Example 476

##### 4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 369 replacing benzyl alcohol with methanol. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCL salt.

MS (APCI +) m/z 409 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.90 (bs, 1H), 8.93 (s, 1H), 8.54 (d, 1H), 8.52 (s, 1H), 7.94 (t, 1H), 7.68 (m, 1H), 7.67 (m, 1H), 7.60 (d, 1H), 7.54 (d, 1H), 4.15 (s, 3H).

#### Example 477

##### 4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared following the procedure in Example 246 replacing dimethylamine with bis(2-ethoxyethyl)amine. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

MS (APCI +) m/z 538 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.11 (bs, 1H), 8.89 (s, 1H), 8.40 (s, 1H), 8.26 (d, 1H), 7.89 (m, 1H), 7.81 (d, 1H), 7.64 (d, 1H), 7.58-7.46 (m, 3H), 3.88 (m, 4H), 3.63 (t, 4H), 3.44 (q, 4H), 1.09 (t, 6H).

#### Example 478

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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4-Hydroxymethyl piperidine was treated sequentially with di-tert-butyl dicarbonate, iodoethane, and trifluoroacetic acid to give 4-ethoxymethyl piperidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

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MS (APCI +) m/z 520 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.08 (bs, 1H), 8.91 (s, 1H), 8.40 (s, 1H), 8.28 (d, 1H), 7.89 (s, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 7.57 (t, 1H), 7.48 (bs, 1H), 4.56 (bd, 2H), 3.40 (q, 2H), 3.24 (d, 2H), 3.11 (t, 2H), 1.92 (m, 1H), 1.81 (d, 2H), 1.22 (m, 2H), 1.18 (t, 3H).

Example 479

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyran)oxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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4-Hydroxymethyl piperidine was treated sequentially with di-tert-butyl dicarbonate, methanesulfonyl chloride, sodium 4-tetrahydropyranoxide, and ethereal HCl to give 4-(4-tetrahydropyran)oxymethyl piperidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCl salt.

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MS (APCI +) m/z 576 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.89 (bs, 1H), 8.88 (s, 1H), 8.44 (s, 1H), 8.24 (d, 1H), 7.89 (t, 1H), 7.81 (m, 1H), 7.64 (m, 1H), 7.57 (t, 1H), 7.50 (d, 1H), 7.31 (bs, 1H), 4.55 (bd, 2H), 3.78 (m, 2H), 3.52-3.22 (m, 5H), 3.07 (t, 2H), 1.89-1.79 (m, 5H), 1.41-1.16 (m, 4H).

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Example 480

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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4-Hydroxymethyl piperidine was treated sequentially with di-tert-butyl dicarbonate, 2-chloroethyl ethyl ether and ethereal HCl to give 4-ethoxyethoxymethyl

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piperidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the HCL salt.

MS (APCI +) m/z 564 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.13 (bs, 1H), 8.90 (s, 1H), 8.33 (s, 1H), 8.29 (d, 1H), 7.88 (s, 1H), 7.81 (d, 1H), 7.74 (d, 1H), 7.63 (d, 1H), 7.54 (t, 1H), 7.50 (s, 1H), 4.55 (bd, 2H), 3.50-3.38 (m, 6H), 3.28 (d, 2H), 3.15 (t, 2H), 1.93 (m, 1H), 1.82 (d, 2H), 1.26 (m, 2H), 1.08 (t, 3H).

#### Example 481

4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxolanemethylamino)-3-pyridazinylpyrido[2,3-d]pyrimidine

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with 2-methylaminomethyl-1,3-dioxolane.

MS (APCI +) m/z 494 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.59 (s, 1H), 8.38 (d, 1H), 8.27 (s, 1H), 7.85-7.77 (m, 2H), 7.62-7.53 (m, 2H), 7.35 (d, 1H), 5.10 (t, 1H), 3.97-3.77 (m, 6H), 3.24 (s, 3H).

#### Example 482

4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decan-8-oxo)-3-pyridazinylpyrido[2,3-d]pyrimidine

Treatment of 1,4-dioxaspiro[4.5]decan-8-one with lithium aluminum hydride in diethyl ether provided 1,4-dioxaspiro[4.5]decan-8-ol which was subsequently treated as in Example 369 replacing benzyl alcohol to give the title compound.

MS (APCI +) m/z 535 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.62 (s, 1H), 8.60 (d, 1H), 8.28 (s, 1H), 7.85-7.77 (m, 2H), 7.60 (m, 2H), 7.40 (d, 1H), 5.42 (m, 1H), 3.90 (s, 4H), 2.10-1.55 (m, 8H).

#### Example 483

5

4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 369 replacing benzyl alcohol with cis 1,3-O-benzylidene glycerol. Treatment with excess 4 M HCl in dioxane followed by

lyophilization gave the title compound as the HCL salt.

MS (APCI +) m/z 469 (M+H)<sup>+</sup>;

15

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.05 (bs, 1H), 8.93 (s, 1H), 8.51 (d, 1H), 8.50 (s, 1H), 7.92 (s, 1H), 7.82 (d, 1H), 7.66 (d, 1H), 7.59 (t, 1H), 7.53 (d, 1H), 4.59 (dd, 2H), 4.45 (dd, 2H), 3.90 (m, 1H), 3.45 (m, 2H).

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Example 484

4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 369 replacing benzyl alcohol with 3-hydroxypyridine. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

MS (APCI +) m/z 472 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.10 (bs, 1H), 8.98 (s, 1H), 8.69 (d, 1H), 8.67 (s, 1H), 8.56 (dd, 1H), 8.51 (s, 1H), 7.93-7.79 (m, 4H), 7.68-7.53 (m, 4H).

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Example 485

4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindole hydrochloride (SALOR) and adding potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

MS (APCI +) m/z 530 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.03 (bs, 1H), 8.93 (s, 1H), 8.46 (s, 1H), 8.30 (d, 1H), 7.92 (m, 1H), 7.83 (dd, 1H), 7.67-7.52 (m, 3H), 7.26 (d, 1H), 4.33 (d, 1H), 3.95-3.32 (m, 4H), 2.78 (m, 1H), 2.66 (m, 1H), 1.72-1.44 (m, 4H), 1.42 (s, 3H).

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Example 486

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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5 Boc-piperidine-4-carboxylic acid was coupled with N-ethylmethoxyethylamine using standard amide formation conditions to give Boc-piperidine-4-(N-ethylmethoxyethyl) carboxamide. This material was treated with HCl and the resulting amine was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane to give the desired product. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

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MS (APCI +) m/z 591 (M+H)<sup>+</sup>;

25

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.00 (bs, 1H), 8.93 (s, 1H), 8.50 (s, 1H), 8.27 (d, 1H), 7.92 (m, 1H), 7.83 (d, 1H), 7.67-7.45 (m, 4H), 4.59 (d, 2H), 3.55-2.95 (12H), 1.80-1.52 (m, 4H), 1.05 (t, 3H).

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Example 487

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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20 The title compound was prepared following the procedure of Example 486 replacing N-ethylmethoxyethylamine with N-methylmethoxyethylamine.

MS (APCI +) m/z 577 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.07 (bs, 1), 8.91 (s, 1H), 8.45 (s, 1H), 8.28 (d, 1H), 7.90 (m, 1H), 7.82 (dd, 1H), 7.67-7.53 (m, 3H), 7.48 (bs, 1H), 4.56 (bd, 1H), 3.62-3.05 (m, 8H), 3.53 (s, 3H), 3.10 (s, 3H), 1.84-1.54 (m, 4H).

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Example 488

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4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypropylidene)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with cis-3,4-bis(methoxymethoxy) pyrrolidine (Rosenberg et al.; J Med Chem 33, 7 (1990) pp1962-1969).

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MS (APCI +) m/z 568 (M+H)<sup>+</sup>;

5 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.58 (s, 1H), 8.40 (d, 1H), 8.26 (s, 1H), 7.85-7.76 (m, 2H), 7.62-7.50 (m, 2H), 7.12 (d, 1H), 4.72 (m, 4H), 4.37 (m, 2H), 3.80 (bm, 2H), 3.63 (bm, 2H), 3.32 (s, 6H).

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#### Example 489

10 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 367 replacing (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane with hexahydro-1H-furo[3,4-c]pyrrole (US Patent 3910950, ICI United States Inc. 1975). Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

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MS (APCI +) m/z 490 (M+H)<sup>+</sup>;

5 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.01 (bs, 1H), 8.93 (s, 1H), 8.48 (s, 1H), 8.30 (d, 1H), 7.90 (m, 1H), 7.84 (m, 1H), 7.65 (m, 1H), 7.57 (t, 1H), 7.48 (bs, 1H), 7.20 (d, 1H), 3.85 (m, 4H), 3.68-3.45 (m, 4H), 3.12 (m, 2H).

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#### Example 490

35 4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

35

Prepared as described for Example 370 replacing 4-methoxypiperidine with hexahydro-1H-furo[3,4-c]pyrrole (US Patent 3910950, ICI United States Inc. 1975). Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

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MS (APCI +) m/z 489 (M+H)<sup>+</sup>;

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<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 9.98 (bs, 1H), 9.03 (d, 1H), 8.88 (s, 1H), 8.67 (dd, 1H), 8.22 (s, 1H), 7.95 (m, 1H), 7.82 (dd, 1H), 7.64 (d, 1H), 7.55 (t, 1H), 7.34 (bs, 1H), 7.03 (d, 1H), 3.90-3.11 (m, 10H).

#### Example 491

##### 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with (anti)-3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int. Appl. (1992) WO<sub>92</sub>10191) and adding potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt. MS (APCI +) m/z 478 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.06 (s, 1H), 8.93 (s, 1H), 8.42 (s, 1H), 8.35 (d, 1H), 7.91 (m, 1H), 7.84 (dd, 1H), 7.65 (dd, 1H), 7.57 (t, 1H), 7.50 (bs, 1H), 7.35 (d, 1H), 4.02 (m, 1H), 3.95-3.30 (m, 5H), 2.27 (m, 1H), 1.05 (d, 3H).

#### Example 492

##### 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 replacing 4-methoxypiperidine with (anti)-3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int. Appl. (1992) WO<sub>92</sub>10191) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt. MS (APCI +) m/z 477 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.12 (bs, 1H), 9.00 (d, 1H), 8.90 (s, 1H), 8.78 (dd, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 7.57 (t, 1H), 7.42 (s, 1H), 7.20 (d, 1H), 4.07-3.30 (m, 6H), 2.30 (m, 1H), 1.03 (d, 3H).

#### Example 493

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane with (anti)-3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int.Appl. (1992) WO<sub>92</sub>10191) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

MS (APCI +) m/z 478 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.18 (bs, 1H), 8.92 (s, 1H), 8.42 (d, 1H), 8.26 (s, 1H), 7.91 (s, 1H), 7.83 (d, 1H), 7.70-7.51 (m, 4H), 4.40-3.64 (m, 5H), 3.30 (t, 1H), 2.38 (m, 1H), 1.18 (d, 3H).

Example 494

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 replacing 4-methoxypiperidine with (syn)-3-hydroxy-4-methylpyrrolidine hydrochloride (PCT Int.Appl. (1992) WO<sub>92</sub>10191) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.

MS (APCI +) m/z 477 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.08 (bs, 1H), 8.97 (d, 1H), 8.90 (s, 1H), 8.78 (dd, 1H), 8.26 (s, 1H), 7.97 (m, 1H), 7.82 (m, 1H), 7.65 (dd, 1H), 7.57 (t, 1H), 7.42 (s, 1H), 7.20 (d, 1H), 4.26 (s, 1H), 4.10-3.22 (m, 5H), 2.38 (m, 1H), 1.08 (d, 3H).

Example 495

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 replacing 4-methoxypiperidine with 3-cyano-4-hydroxypyrrolidine hydrochloride (Hong et al.; J Med Chem. 40, 22. (1997) pp 3584-3593) and potassium carbonate. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCL salt.



MS (ESI +) m/z 488 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.03 (bs, 1H), 9.08 (d, 1H), 8.88 (s, 1H), 8.65 (t, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.82 (d, 1H), 7.62 (d, 1H), 7.55 (t, 1H), 7.32 (d, 1H), 7.00 (d, 1H), 4.65 (m, 1H), 4.15-3.50 (m, 6H).

#### Example 496

##### 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

The compound was isolated from the reaction mixture of Example 495. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

MS (ESI +) m/z 562 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.03 (bs, 1H), 9.05 (d, 1H), 8.52 (s, 1H), 8.44 (dd, 1H), 7.85-7.76 (m, 3H), 7.57-7.51 (m, 3H), 7.32 (s, 1H), 6.60 (d, 1H), 5.28 (d, 1H), 4.56 (m, 1H), 3.70-3.25 (m, 4H), 3.03 (m, 1H), 1.27 (s, 9H).

#### Example 497

##### 4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

A solution of (S)-1-Boc-2-pyrrolidinemethanol and triethylamine in dichloromethane at 0 °C was treated with methanesulfonyl chloride. The resulting mesylate was treated with 1.5 eq each of 4-hydroxytetrahydropyran and powdered potassium hydroxide in DMSO to afford the tetrahydropyranyl ether. Deprotection of the Boc amine with trifluoroacetic acid provided the free base pyrrolidine which was reacted as in Example 367 replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

MS (ESI +) m/z 562 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.00 (bs, 1H), 8.93 (s, 1H), 8.49 (s, 1H), 8.30 (d, 1H), 7.91 (m, 1H), 7.84 (m, 1H), 7.64 (m, 1H), 7.58 (t, 1H), 7.49 (bs, 1H), 7.27 (bd, 1H), 4.45 (m, 1H), 3.78-3.25 (m, 9H), 2.04 (m, 4H), 1.78 (m, 2H), 1.37 (m, 2H).

#### Example 498

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydro-2H-pyran-4-yl)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Equimolar amounts of 1-N-Boc-pyrrolidinone and O-(tetrahydro-2H-pyran-4-yl)hydroxylamine hydrochloride (JP 07173169 Takeda Chemical Industries Ltd (1995)) were heated at reflux in 1:1 ethanol/pyridine, cooled and concentrated to give after silica gel chromatography the desired Boc protected oxime. Deprotection with trifluoroacetic acid afforded the free base pyrrolidine which was treated as in Example 367, replacing (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane. Treatment with excess 4 M HCl in dioxane followed by lyophilization gave the title compound as the di-HCl salt.

MS (ESI +) m/z 561 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.11 (bs, 1H), 8.92 (s, 1H), 8.41 (d, 1H), 8.35 (dd, 1H), 7.90 (d, 1H), 7.83 (m, 1H), 7.65-7.33 (m, 4H), 4.38 (d, 2H), 4.25 (m, 1H), 4.10-3.72 (m, 4H), 3.44 (m, 2H), 2.93 (m, 2H), 1.93 (m, 2H), 1.55 (m, 2H).

#### Example 500

4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 except substituting 2-acetyl-5-bromothiophene (Lancaster) for 5-acetyl-2-morpholinylthiazole.

MS (DCI/NH<sub>3</sub>) m/z 463/465 (M+H)<sup>+</sup>;

IR (microscope) 3473, 3299, 1580, 1557, 1073 cm<sup>-1</sup>.

#### Example 501

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 except substituting 3-acetyl-2,5-dimethylthiophene (Acros) for 5-acetyl-2-morpholinylthiazole.

mp: 210-212 °C;  
MS (DCI/NH<sub>3</sub>) m/z 411/413 (M+H)<sup>+</sup>;  
IR (microscope) 3477, 3058, 1555, 1574, 1142 cm<sup>-1</sup>.

#### Example 502

4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 except substituting 2-acetyl-5-chlorothiophene (Acros) for 5-acetyl-2-morpholinylthiazole.

mp: 264-265 °C;  
MS (DCI/NH<sub>3</sub>) m/z 417/419 (M+H)<sup>+</sup>;  
IR (microscope) 3466, 3290, 1635, 1561, 1114 cm<sup>-1</sup>.

#### Example 503

4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 except substituting 5-acetyl-2,4-dimethylthiazole (Acros) for 5-acetyl-2-morpholinylthiazole.

mp: 254-255 °C; MS (DCI/NH<sub>3</sub>) m/z 412/414 (M+H)<sup>+</sup>;  
IR (microscope) 3477, 3299, 1648, 1563, 1285 cm<sup>-1</sup>.

#### Example 504

4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in 357 except substituting 2-acetyl-5-methylthiophene (Lancaster) for 5-acetyl-2-morpholinylthiazole.

MS (DCI/NH<sub>3</sub>) m/z 397/399 (M+H)<sup>+</sup>;  
IR (microscope) 3294, 3218, 1618, 1581, 1065 cm<sup>-1</sup>.

#### Example 505

4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine

Procedure as found in 357 except substituting 2-acetylfuran (Aldrich) for 5-acetyl-2-morpholinylthiazole. MS (DCI/NH<sub>3</sub>) m/z 367/369 (M+H)<sup>+</sup>;

IR (microscope) 3485, 3110, 1642, 1563, 1008 cm<sup>-1</sup>.

Example 506

4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in 357 substituting 4,4-dioxyethylenepiperidine (Aldrich) for morpholine in Example 357a.

mp: >285 °C; MS (DCI/NH<sub>3</sub>) m/z 525/527 (M+H)<sup>+</sup>;

IR (microscope) 3493, 3087, 1648, 1584, 1142 cm<sup>-1</sup>.

Example 507

4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting 3-acetylthiophene (Aldrich) for the product from Example 357b in 357c. MS (DCI/NH<sub>3</sub>) m/z 383/385 (M+H)<sup>+</sup>; IR

(microscope) 3473, 3100, 1638, 1561, 1288 cm<sup>-1</sup>.

Example 508

4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting 2-acetyl-3-methylthiophene (Lancaster) for the product from Example 357b in Example 357c. mp: 271-272 °C; MS (DCI/NH<sub>3</sub>) m/z 397/399 (M+H)<sup>+</sup>; IR (microscope) 3470, 3060, 1644, 1560, 1123 cm<sup>-1</sup>.

Example 509

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 509c for the product from 357b in 357c to give the title compound. mp: 278-282 °C; MS (DCI/NH<sub>3</sub>) m/z 469/471 (M+H)<sup>+</sup>; IR (microscope) 3468, 3085, 1653, 1559, 1116 cm<sup>-1</sup>.

509a: 1-Bromobutane-2,3-dione-3-oxime

2,3-butanedione (30 mL, 355 mmol; Aldrich) at 0 °C was treated with 10 drops of bromine (caution: delayed exothermic reaction). After 20 minutes, additional bromine (12.2 mL, 237 mmol) was added dropwise at such a rate as to maintain reaction temperature between 20-30 °C. Vacuum distillation (10 mmHg; fractions between 37-48 °C) provided 16.26 g (41%) of 1-bromo-2,3-butanedione compound as a yellow oil. A solution of 1-bromo-2,3-butanedione (16.26 g, 98.55 mmol) in water at 0 °C was treated dropwise with a solution of hydroxylamine hydrochloride (6.90 g, 99.29 mmol) and sodium carbonate (4.20 g, 39.63 mmol) in water (38 mL). After 1 hour, the reaction was extracted with dichloromethane, concentrated to one fourth the original volume, cooled and filtered to provide 7.08 g (40%) of the desired compound as an unstable (freezer) white solid.

509b: 1-(2-Morpholinothiazol-5-yl)ethanoneoxime

A solution of known morpholine-4-carbothioic acid amide (2.66 g, 18.2 mmol; J. Het. Chem. 1987, 24, 1509) and the product from Example 509a (3.29 g, 18.3 mmol) in ethanol (5.5 mL) was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and the solid filtered, washed with ethanol and dried to provide 4.16 g (99%) of the desired compound as pink solid. MS (DCI/NH<sub>3</sub>) m/z 228 (M+H)<sup>+</sup>.

509c: 1-(2-Morpholinothiazol-5-yl)ethanone

A solution of the product from Example 509b (6.00 g, 26.4 mmol) in water (250 mL), sulfuric acid (27 mL) and ethanol (26 mL) at 50 °C was treated dropwise with sodium nitrite (1.97 g, 28.5 mmol) as a solution in water (50 mL). After 2 hours, the mixture was cooled to 0 °C, neutralized with ammonium hydroxide and extracted with dichloromethane. The organic phases were concentrated and purified by silica gel chromatography (elution with 10% ethyl acetate/dichloromethane) to give 1.06 g (19%) the desired compound as a pink solid. MS (DCI/NH<sub>3</sub>) m/z 213 (M+H)<sup>+</sup>.

Example 510

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazol)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 510a for the product from Example 357a in Example 357b to give the title compound. mp: 277-278 °C; MS (DCI/NH<sub>3</sub>) m/z 537/539 (M+H)<sup>+</sup>; IR (microscope) 3481, 3061, 1607, 1544, 1116 cm<sup>-1</sup>.

step a: 2-Morpholino-4-trifluoromethylthiazole

Procedure as found in Example 509b substituting 3-bromo-1,1,1-trifluoroacetone (Aldrich) for the product from Example 509a. MS (DCI/NH<sub>3</sub>) m/z 239 (M+H)<sup>+</sup>.

Example 511

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in 357 substituting the product from Example 511a for the product from Example 357b in Example 357c. mp: 265 °C (dec); MS (ESI) m/z 468/470 (M+H)<sup>+</sup>; IR (microscope) 3484, 3052, 1647, 1581, 1118 cm<sup>-1</sup>.

511a: 5-Acetyl-2-morpholinothiophene

A solution of 5-acetyl-2-bromothiophene (8.01 g, 39.1 mmol; Aldrich) and morpholine (16 mL) was heated to 145 °C overnight. The reaction mixture was cooled and partitioned between water and dichloromethane. The organic phase was concentrated and purified by silica gel chromatography (elution with 30% hexane/ethyl acetate) to give 5.61 g (68%) of the desired compound. MS (DCI/NH<sub>3</sub>) m/z 212 (M+H)<sup>+</sup>.

Example 512

4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazol)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 357a for the product from Example 357a in Example 357b to provide the title compound. mp:

>280 °C; MS (DCI/NH<sub>3</sub>) m/z 483/485 (M+H)<sup>+</sup>; IR (microscope) 3481, 3078, 1653, 1510, 1117 cm<sup>-1</sup>.

512a: 4-Methyl-2-morpholinothiazole

Procedure as in Example 509b substituting chloroacetone (Aldrich) for the product from 509a. MS (DCI/NH<sub>3</sub>) m/z 185 (M+H)<sup>+</sup>.

Example 513

4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting 3-acetyl-2,5-dichlorothiophene (Aldrich) for the product from Example 357b in Example 357c to provide the title compound. mp: 258-259 °C; MS (DCI/NH<sub>3</sub>) m/z 451/453 (M+H)<sup>+</sup>; IR (microscope) 3477, 3060, 1651, 1564, 1044 cm<sup>-1</sup>.

Example 514

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting 3-acetyl-2,5-dimethylfuran (Lancaster) for the product from Example 357b in Example 357c to provide the title compound. MS (DCI/NH<sub>3</sub>) m/z 395/397 (M+H)<sup>+</sup>; IR (microscope) 3492, 3092, 1641, 1581, 1222 cm<sup>-1</sup>.

Example 515

4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine

A solution of the product from Example 515a (3.30 g, 9.34 mmol) and triethylorthoformate (20 mL) was treated with a catalytic amount of ammonium sulfate and heated to 100 °C for 2 hours. The reaction mixture was cooled, treated with ammonia (2 M in ethanol, 50 mL) and stirred overnight. The dark mixture was then treated with sodium methoxide (3 M in methanol, 30 mL) and heated to reflux for 3 hours. The reaction was cooled, concentrated and the residue taken up in water and neutralized with 10% hydrochloric acid. The aqueous phase was extracted with dichloromethane, the

organic phase concentrated and purified by silica gel chromatography (elution with 5% methanol/dichloromethane) to provide 830 mg (23%) of the title compound. MS (DCI/NH<sub>3</sub>) m/z 380/382 (M+H)<sup>+</sup>; IR (microscope) 3482, 3051, 1643, 1580, 1073 cm<sup>-1</sup>.

515a: 4-(3-Bromophenyl)-3-cyano-6-(2-(N-methylpyrrole)pyridine-2-amine

Procedure as found in Example 357c substituting 2-acetyl-1-methylpyrrole for the product from 357b.

MS (DCI/NH<sub>3</sub>) m/z 353/355 (M+H)<sup>+</sup>.

Example 516

4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting dimethylamine (40% in water, Aldrich) for morpholine in Example 357a. mp: >280 °C; MS (DCI/NH<sub>3</sub>) m/z 427/429 (M+H)<sup>+</sup>; IR (microscope) 3455, 3054, 1636, 1503, 1035 cm<sup>-1</sup>.

Example 517

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 515 substituting thiomorpholine for morpholine in Example 357a to provide the title compound. MS (DCI/NH<sub>3</sub>) m/z 485/487 (M+H)<sup>+</sup>; IR (microscope) 3474, 3083, 1641, 1509, 1129 cm<sup>-1</sup>.

Example 518

4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

A solution of the product from Example 517 (402 mg, 0.83 mmol) in acetic acid and acetone was treated with potassium permanganate in water until complete consumption of starting material was detected. Reaction mixture poured over ice, the solution made strongly basic with 50% sodium hydroxide. The resulting solid was filtered and purified by silica gel chromatography (elution with 5% methanol/dichloromethane) to



provide 231 mg (54%) of the title compound as a yellow solid. MS (DCI/NH<sub>3</sub>) m/z 517/519 (M+H)<sup>+</sup>; IR (microscope) 3484, 3056, 1606, 1501, 1125 cm<sup>-1</sup>.

#### Example 519

4-amino-5-(3-bromophenyl)-7-(1-N-methyl-2-morpholinyl-5-imidazolyl)pyrido[2,3-d]pyrimidine

Procedure as in Example 515 substituting the product from Example 519a for the product of Example 357b in Example 357c. MS (DCI/NH<sub>3</sub>) m/z 466/468 (M+H)<sup>+</sup>; IR (microscope) 3479, 3089, 1646, 1587, 1118 cm<sup>-1</sup>.

#### 519a: 4-Acetyl-1-methyl-2-morpholinylimidazole

A solution of 5-acetyl-2-aminooxazole (7.00 g, 55.5 mmol; J. Org. Chem. 1984, 49, 566) and morpholine (20 mL) in water (14 mL) was heated to reflux overnight. The reaction was cooled to room temperature, concentrated and triturated with ethyl acetate, filtered and dried to provide 3.52 g (33%) of the desired compound. A slurry of sodium hydride (60% in oil, 590 mg, 14.7 mmol) and methyl iodide (0.86 mL, 13.7 mmol) in tetrahydrofuran (20 mL) at room temperature was added a solution of 4-acetyl-2-morpholinylimidazole (2.44 g, 12.5 mmol) in dimethylformamide (13 mL) and stirring continued for 1.5 hours. Reaction quenched with ethanol, water added and extracted with dichloromethane. The organic phases were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue purified by silica gel chromatography (elution with 25% dichloromethane/ethyl acetate) to provide 1.27 g (49%) of the desired compound. MS (DCI/NH<sub>3</sub>) m/z 210 (M+H)<sup>+</sup>.

#### Example 520

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazolyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product for Example 520a for the product of Example 357b in Example 357c. MS (DCI/NH<sub>3</sub>) m/z 453/455 (M+H)<sup>+</sup>; IR (microscope) 3502, 3388, 1607, 1575, 1116 cm<sup>-1</sup>.

520a: 5-Acetyl-2-morpholinooxazole

A solution of 2-bromo-3-oxobutyr aldehyde (6.00 g, 36.4 mmol; Bull. Chem. Soc. Jpn. 1965, 38, 1158) and morpholine-4-carboxylic acid amide (9.01 g, 69.2 mmol; J. Am. Chem. Soc. 1945, 67, 1055) in acetone (40 mL) was stirred at room temperature for 1 hour then at reflux for 1 hour. The solvent removed in vacuo and the residue purified by silica gel chromatography (gradient elution with 10% ethyl acetate/dichloromethane to ethyl acetate) to provide 2.85 g (40%) of the desired compound as a yellow solid. MS (DCI/NH<sub>3</sub>) m/z 197 (M+H)<sup>+</sup>.

## Example 521

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazovl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 521b for the product from Example 357b in Example 357c. MS (DCI/NH<sub>3</sub>) m/z 471/473 (M+H)<sup>+</sup>; IR (microscope) 3472, 3051, 1645, 1519, 1090 cm<sup>-1</sup>.

521a: 2-(N-methyl-N-(2-methoxy)ethylamino)thiazole

Procedure as found in Example 357a substituting (2-methoxyethyl)methylamine (TCI Japan) for morpholine. MS (DCI/NH<sub>3</sub>) m/z 173 (M+H)<sup>+</sup>.

521b: 5-Acetyl-2-(N-methyl-N-(2-methoxy)ethylamino)thiazole

A solution of the product from Example 521a (4.98 g, 28.9 mmol) in tetrahydrofuran (150 mL) at -78 °C was treated with n-BuLi (2.3 M in hexanes, 15 mL) and stirring continued for 40 minutes. The light yellow solution was then treated with acetaldehyde (9.00 mL, 161 mmol), stirred for 15 minutes, quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was taken up in dichloromethane (150 mL) and treated with manganese dioxide (5 weight equivalents) and heated to reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated to provide 4.62 g (75%) of the desired compound. MS (DCI/NH<sub>3</sub>) m/z 215 (M+H)<sup>+</sup>.

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Example 522

10

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

15

5 Procedure as found in Example 357 substituting methylethyl amine (Aldrich) for (2-methoxyethyl)methylamine in Example 521a. MS (DCI/NH<sub>3</sub>) m/z 441/443 (M+H)<sup>+</sup>; IR (microscope) 3493, 3041, 1655, 1524, 1133 cm<sup>-1</sup>.

Example 523

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10 4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine

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Procedure as found in Example 357 substituting pyrrolidine (Aldrich) for (2-methoxyethyl)methylamine in Example 521a. MS (DCI/NH<sub>3</sub>) m/z 453/455 (M+H)<sup>+</sup>; IR (microscope) 3483, 3044, 1647, 1511, 1203 cm<sup>-1</sup>.

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Example 524

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4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting methylpropyl amine (Aldrich) for (2-methoxyethyl)methylamine in Example 521a to provide the title compound.

35

20 MS (DCI/NH<sub>3</sub>) m/z 455/457 (M+H)<sup>+</sup>; IR (microscope) 3489, 3042, 1646, 1518, 1139 cm<sup>-1</sup>.

Example 525

40

4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as in Example 357 substituting diethylamine (Aldrich) for morpholine in Example 357a to provide the title compound. MS (DCI/NH<sub>3</sub>) m/z 455/457 (M+H)<sup>+</sup>; IR (microscope) 3478, 3051, 1582, 1518, 1177 cm<sup>-1</sup>.

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Example 526

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30 4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

55

Procedure as in Example 515 substituting the product from Example 526a for the product of Example 357b in Example 357c provided the title compound. MS (DCI/NH<sub>3</sub>) m/z 482/484 (M+H)<sup>+</sup>; IR (microscope) 3469, 3053, 1645, 1500, 1002 cm<sup>-1</sup>.

526a: 5-Acetyl-2-(4-methylpiperazine)thiazole

A solution of silicon tetrathioisocyanate (2.02 g, 7.76 mmol; Can. J. Chem. 1963, 41, 2123) in toluene (30 mL) was treated with a solution of N-methylpiperazine (3.50 mL, 31.6 mmol; Acros) in toluene (10 mL) and the mixture heated to 80 °C for 20 minutes. The resulting mixture was concentrated, taken up in 10% water in isopropanol, refluxed for 20 minutes, cooled and filtered. The filtrate was concentrated and recrystallized from isopropanol to provide 3.89 g (77%) of the desired compound. A solution of the 4-methylpiperazine-1-carbothioic acid amide (3.53 g, 22.2 mmol) and 2-bromo-3-oxobutylaldehyde (3.69 g, 22.2 mmol; Bull. Chem. Soc. Jpn. 1965, 38, 1158) in acetone was refluxed for 30 minutes. The reaction mixture was cooled, quenched with saturated aqueous sodium carbonate and extracted with dichloromethane. The organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue purified by silica gel chromatography (gradient elution with 30% acetone/dichloromethane to 5% methanol/dichloromethane) to provide 1.76 g (35%) of the desired compound as a yellow-brown solid.

Example 527

4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as in Example 515 substituting 1-(2-pyridyl)piperazine (Acros) for N-methylpiperazine in Example 526a. MS (ESI) m/z 545/547 (M+H)<sup>+</sup>; IR (microscope) 3484, 3049, 1651, 1495, 1053 cm<sup>-1</sup>.

Example 528

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-(2-pyridylethyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

Procedure as in Example 515 substituting 2-(2-(methylamino)ethyl)pyridine dihydrochloride (Acros) for N-methylpiperazine in Example 526a. MS (DCI/NH<sub>3</sub>) m/z 518/520 (M+H)<sup>+</sup>; IR (microscope) 3472, 3054, 1648, 1517, 1051 cm<sup>-1</sup>.

#### Example 529

##### 4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

A solution of the product from Example 506 (900 mg, 1.71 mmol) and tetrahydrofuran (12 mL) at room temperature was treated with 3 N hydrochloric acid (12 mL) and stirring continued for 24 hours. The reaction was made basic with sodium bicarbonate, extracted with dichloromethane, concentrated and the residue purified by silica gel chromatography (elution with 5% methanol/dichloromethane) to provide 263 mg (32%) of the title compound. MS (DCI/NH<sub>3</sub>) m/z 481/483 (M+H)<sup>+</sup>; IR (microscope) 3482, 3084, 1716, 1508, 1074 cm<sup>-1</sup>.

#### Example 530

##### 4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine

A solution of Example 529 (200 mg, 0.415 mmol) and 4-aminomorpholine (Aldrich) in ethanol (5 mL) was heated to reflux for 5 hours. The solid was filtered and dried to provide 140 mg (60%) of the title compound. MS (DCI/NH<sub>3</sub>) m/z 565/567 (M+H)<sup>+</sup>; IR (microscope) 3485, 3051, 1644, 1506, 1111 cm<sup>-1</sup>.

#### Example 531

##### 4-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine

Procedure as found in Example 357 substituting the product from Example 531b for the product from Example 357b in Example 357c. MS (DCI/NH<sub>3</sub>) m/z 527/529 (M+H)<sup>+</sup>; IR (microscope) 3439, 3058, 1639, 1609, 1072 cm<sup>-1</sup>.

531a: 5-Acetyl-2-thiopyridine

A solution of 5-acetyl-2-chloropyridine (10.11 g, 64.98 mmol; Tetrahedron 1992, 48, 9233) in ethanol was treated with thiourea (5.97 g, 78.4 mmol) and heated to reflux overnight. The reaction was cooled, the solid collected and taken up in 2 M sodium hydroxide. After stirring for 2 hours, the red solid was collected, acidified with glacial acetic acid. The yellow solid was collected and recrystallized from ethanol to provide 3.39 g (34%) of the desired compound.

MS (DCI/NH<sub>3</sub>) m/z 154 (M+H)<sup>+</sup>.

531b: 5-Acetyl-2-morpholinopyridylsulfonamide

A suspension of the product from Example 531a (7.01 g; 45.7 mmol) in 1 M hydrochloric acid (60 mL) was treated with chlorine gas at 0 °C for 1 hour. The resulting solid was filtered, and taken up in dichloromethane (50 mL) and treated with morpholine (15 mL). After 1 hour, the mixture was quenched with 1 N hydrochloric acid and extracted with dichloromethane. The organic phases were combined, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was recrystallized from ethyl acetate to provide 6.31 g (59%) of the desired compound. MS (DCI/NH<sub>3</sub>) m/z 271 (M+H)<sup>+</sup>.

Example 532

4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 529 substituting the product from Example 533c for the product from Example 506. MS (DCI/NH<sub>3</sub>) m/z 476/478 (M+H)<sup>+</sup>; IR (microscope) 3469, 3051, 1644, 1561, 1108 cm<sup>-1</sup>.

Example 533

4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 515 substituting the product from Example 533b for the product from Example 357b in Example 357c and formation of the salt by treatment with HCl in diethyl ether to provide the title compound. MS (DCI/NH<sub>3</sub>) m/z 520/522 (M+H)<sup>+</sup>; IR (microscope) 3434, 3064, 1645, 1602, 1105 cm<sup>-1</sup>.

533a: 5-bromo-2-(1,4-dioxo-8-azaspiro[4.5]decane)pyrimidine

A solution of 5-bromo-2-chloropyrimidine (3.09 g, 16.0 mmol; J. Chem. Soc. Chem. Commun. 1996, 2719) in ethanol (20 mL) at room temperature was treated with 1,4-dioxo-8-azaspiro[4.5]decane (6.00 mL, 46.8 mmol; Aldrich) and stirring continued overnight. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic phases were combined, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated and the residue purified by silica gel column chromatography (elution with 25% ethyl acetate/hexanes) to provide 4.78 g (99%) of the desired compound as a white solid. MS ( $\text{DCI}/\text{NH}_3$ )  $m/z$  300/302 ( $\text{M}+\text{H}$ ) $^+$ .

533b: 5-Acetyl-2-(1,4-dioxo-8-azaspiro[4.5]decane)pyrimidine

Procedure as found in Example 521b substituting the product from Example 533a for Example 521a to provide the desired compound. MS ( $\text{DCI}/\text{NH}_3$ )  $m/z$  264 ( $\text{M}+\text{H}$ ) $^+$ .

Example 5344-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl)pyridof[2,3-d]pyrimidine

Procedure as found in Example 515 substituting the product from Example 534b for the product from Example 357b in Example 357c and formation of the salt by treatment with HCl in diethyl ether to provide the title compound. MS ( $\text{DCI}/\text{NH}_3$ )  $m/z$  520/522 ( $\text{M}+\text{H}$ ) $^+$ ; IR (microscope) 3292, 3060, 1634, 1526, 1105  $\text{cm}^{-1}$ .

534a: 5-Acetyl-2-chloropyrazine

A solution of 5-hydroxypyrazine-2-carboxylic acid (5.29 g, 37.76 mmol) in toluene was treated with thionyl chloride (9.00 mL, 123 mmol) and the mixture heated to reflux for 16 hours. The reaction mixture was concentrated and the residue taken up in dichloromethane (200 mL) and treated with a solution of N,O-dimethylhydroxylamine hydrochloride in 2 N sodium hydroxide. After 30 minutes, the layers were separated, the organic phase dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. A portion of the amide (807 mg, 4.00

mmol) was taken up in tetrahydrofuran (20 mL) cooled to -10 °C and treated with methylmagnesium bromide (3 M in diethyl ether, 4.00 mL) and warmed to room temperature. The mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to provide 610 mg (97%) of the desired compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 9.00 (d, J = 1.1 Hz, 1 H), 8.63 (d, J = 1.1 Hz, 1 H), 2.70 (s, 3 H).

534b: 5-Acetyl-2-(1,4-dioxo-8-azaspiro[4.5]decane)pyrazine

Procedure as found in Example 511a substituting the product from Example 534a for 5-acetyl-2-bromothiophene and 1,4-dioxo-8-azaspiro[4.5]decane for morpholine. MS (DCI/NH<sub>3</sub>) m/z 264 (M+H)<sup>+</sup>.

Example 535

4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 529 substituting the product from Example 534c for the product from Example 506 to provide the title compound. MS (DCI/NH<sub>3</sub>) m/z 476/478 (M+H)<sup>+</sup>; IR (microscope) 3470, 3085, 1721, 1542, 1184 cm<sup>-1</sup>.

Example 536

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine

Procedure as found in Example 534c substituting cyclopropyl amine (Aldrich) for morpholine in Example 534b. MS (DCI/NH<sub>3</sub>) m/z 497/357 (M+H)<sup>+</sup>; IR (microscope) 3441, 3059, 1640, 1609, 1177 cm<sup>-1</sup>.

Example 537

4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine



Procedure as found in Example 534 substituting 1,4-dioxo-8-azaspiro[4,5]decane (Aldrich) for morpholine in Example 534b. MS (DCI/NH<sub>3</sub>) m/z 583/585 (M+H)<sup>+</sup>; IR (microscope) 3483, 3060, 1567, 1355, 1101 cm<sup>-1</sup>.

#### Example 538

4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine

Procedure as found in Example 530 substituting the product from 532 for the product from Example 529 and O-(tetrahydro-2H-pyran-4-yl)hydroxylamine hydrochloride (JP07173169; CAN 123:313629) for 4-aminomorpholine. MS (DCI/NH<sub>3</sub>) m/z 575/577 (M+H)<sup>+</sup>; IR (microscope) 3486, 3055, 1601, 1515, 1345 cm<sup>-1</sup>.

#### Example 539

4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359, substituting O-Benzylhydroxylamine hydrochloride for ethoxyamine hydrochloride.

MS (DCI/NH<sub>3</sub>) m/z 580/582 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3486, 3297, 3060, 1603, 1579, 1557 cm<sup>-1</sup>.

#### Example 540

4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butylloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359, substituting O-(tert-butyl)hydroxylamine hydrochloride for ethoxyamine hydrochloride.

MS (DCI/NH<sub>3</sub>) m/z 546/548 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3488, 3301, 3037, 1602, 1560, 1512 cm<sup>-1</sup>.

#### Example 541

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4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 359, substituting O-Cyclohexylhydroxylamine hydrochloride, synthesized by the procedure of Grochowski, E; Jurczak, J. Synthesis 1976, 682 and starting with cyclohexanol, for ethoxyamine hydrochloride.

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MS (DCI/NH<sub>3</sub>) m/z 572/574 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3485, 3297, 2931, 1555, 1517, 1349 cm<sup>-1</sup>.

Example 542

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 359, substituting Hydroxylamine hydrochloride for ethoxyamine hydrochloride.

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MS (DCI/NH<sub>3</sub>) m/z 490/492 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3444, 3020, 2819, 1646, 1605, 1546 cm<sup>-1</sup>.

Example 543

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 359, substituting 4-tetrahydropyranyloxyamine hydrochloride, synthesized by the procedure of Grochowski, E; Jurczak, J. Synthesis 1976, 682 and starting with Tetrahydro-4H-pyran-4-ol, for ethoxyamine hydrochloride. MS (DCI/NH<sub>3</sub>) m/z 574/576 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3484, 3297, 3157, 2954, 1582, 1555 cm<sup>-1</sup>.

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Example 544

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4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359, substituting O-(2-methoxyethyl)hydroxylamine hydrochloride, synthesized by the procedure of Grochowski.

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E; Jurczak. J. Synthesis 1976, 682 and starting with 2-Methoxyethanol, for ethoxyamine hydrochloride.

MS (DCI/NH<sub>3</sub>) m/z 548/550 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3485, 3298, 3042, 1582, 1555, 1517 cm<sup>-1</sup>.

#### Example 545

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 359, substituting O-(2-thienylmethyl)hydroxylamine hydrochloride, synthesized by the procedure of Grochowski, E; Jurczak. J. Synthesis 1976, 682 and starting with 2-Thiophenemethanol, for ethoxyamine hydrochloride.

MS (DCI/NH<sub>3</sub>) m/z 586/588 (M+H; <sup>79</sup>Br/<sup>81</sup>Br); IR (microscope) 3485, 3298, 3068, 1579, 1556, 1507 cm<sup>-1</sup>.

#### Example 546

4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxofuranyl)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-(4'-(5'H-2-oxofuranyl)-4-hydroxypiperidine for 4-methoxypiperidine, which was made as follows: to a solution of 4-bromo-2-triisopropylsiloxyfuran (5.0 g, 15.7 mmol; made according to G. Jas, Synthesis 1991, 965) in THF (50 mL) at -78 °C, a solution of t-butyllithium (1.7 M, 15 mL, 25.5 mmol) was added dropwise for 40 min. A solution of N-benzylpiperidin-4-one (4.4 mL, 23.8 mmol) was added at -78 °C. The reaction mixture was then allowed to warm up over night. Standard work-up. Column chromatographic separation (SiO<sub>2</sub>, ethyl acetate : hexane = 1 : 2) gave 4.72 g product (70%). The product was then deprotected under H<sub>2</sub> in the presence of Pd(OH)<sub>2</sub>, Et<sub>3</sub>N in methanol.

MS (ESI): 559/561 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3432, 3309, 3204, 2928, 1744, 1634, 1605, 1372 cm<sup>-1</sup>

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Example 547 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 559 except substituting Example 548 for Example 562.

MS (ESI): 619/621 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

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IR (Mic): Vmax: 3485, 3310, 3204, 2955, 2849, 1682, 1615, 1578, 1552, 1461, 1353, 1135, 1066 cm<sup>-1</sup>.

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Example 548

4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 367 except substituting 4-acetyl-4-hydroxypiperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, which was prepared as described in Example 562.

MS (ESI): 520/522 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

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IR (Mic): Vmax: 3472, 3385, 3298, 3090, 2953, 1711, 1644, 1578, 1562, 1483, 1464, 1353 cm<sup>-1</sup>.

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Example 549 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared from Example 562 as described in Example 559; substituting carboxymethoxylamine (Aldrich) for 4-tetrahydropyranyloxamine hydrochloride in isopropanol as solvent

MS (ESI): 634/636 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

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IR (Mic): Vmax: 3450, 3311, 3174, 3068, 2984, 2937, 1737, 1674, 1647, 1606, 1555, 1440, 1373, 1201, 1136 cm<sup>-1</sup>.

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Example 550

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridylpyrido[2,3-d]pyrimidine

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Prepared from Example 562 as described in Example 559; substituting  
5 carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in ethanol as solvent.

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MS (ESI): 620/622 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3449, 3313, 3178, 3066, 2985, 1745, 1674, 1648, 1607, 1444, 1371, 1200, 1135 cm<sup>-1</sup>.

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Example 551

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridylpyrido[2,3-d]pyrimidine

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Prepared from Example 562 as described in Example 559; substituting  
15 carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in methanol as solvent.

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MS (ESI): 606/608 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3450, 3309, 3067, 2957, 2933, 1751, 1675, 1647, 1605, 1439, 1368, 1200, 1134 cm<sup>-1</sup>.

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Example 552

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyran-2-yl)hydroxypiperidinyl)-3-pyridylpyrido[2,3-d]pyrimidine

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Prepared from Example 562 as described in Example 559; substituting O-  
25 (tetrahydro-2H-pyran-2-yl)hydroxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

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MS (ESI): 618/620 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3449, 3306, 3197, 3066, 2949, 2872, 1675, 1648, 1607, 1442, 1370, 1200, 1135 cm<sup>-1</sup>.

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Example 553 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting 2-propen-1-oxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 574/576 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3450, 3309, 3175, 3071, 2930, 2871, 1673, 1647, 1605, 1515, 1435, 1200, 1134 cm<sup>-1</sup>.

Example 554 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting ethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride

MS (ESI): 562/564 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3451, 3311, 3063, 2979, 2936, 2881, 1673, 1647, 1606, 1368, 1200, 1183, 1133 cm<sup>-1</sup>.

Example 555 0.6)

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting methoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 548/550 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3450, 3312, 3064, 2965, 2820, 1674, 1646, 1444, 1369, 1199, 1135, 1045 cm<sup>-1</sup>.

Example 556 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as described in Example 559; substituting hydroxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 534/536 (M+H: <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3448, 33133198, 3070, 2881, 1782, 1676, 1650, 1610, 1448, 1371, 1200, 1137 cm<sup>-1</sup>.

#### Example 557

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 328 as described in Example 559; substituting O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride.

MS (ESI): 574/576 (M+H: <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3437, 3304, 3057, 2955, 2859, 2684, 1639, 1605, 1441, 1368, 1238, 1068 cm<sup>-1</sup>.

#### Example 558

4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 328 as described in Example 559; substituting Example 328 for Example 562 and substituting carboxymethoxylamine (Aldrich) for 4-tetrahydropyranoxyamine hydrochloride in isopropanol as solvent.

MS (ESI): 590/592 (M+H: <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3487, 3389, 3301, 3152, 3058, 2979, 2928, 2873, 1749, 1603, 1580, 1557, 1508, 1414, 1348, 1233, 1101 cm<sup>-1</sup>.

#### Example 559

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 562 as follows: to a solution of Example 562 (250 mg, 0.48 mmol) in ethanol (10 mL), 4-tetrahydropyranoxyamine hydrochloride (80 mg, 0.5 mmol; made as described from: JP 94-177353 19940729 and prepared in Example 543)

was added, followed by concentrated HCl (2 drops). The mixture was heated to reflux for about 10 hours. Standard work up, followed by chromatography (SiO<sub>2</sub>, 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) gave 156 mg (53%) of the title compound.

MS (ESI): 618/620 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3488, 3304, 3199, 2954, 2855, 1603, 1578, 1557, 1509, 1352, 1233, 1066 cm<sup>-1</sup>.

#### Example 560

##### 4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-(4-hydroxypiperidin-4-yl)butanolactone for 4-methoxypiperidine, which was made as follows: to a solution of 3-ethoxycarboxylpropyl triphenylphosphonium bromide (10.0 g, 22 mmol) in THF, a solution of potassium bis(trimethylsilyl)amide (0.5 M, 52 mL, 26 mmol) was added at -78 °C. the reaction mixture was allowed to stir for 40 min at -78 °C. N-benzyl-4-piperidinone (4.5 mL, 24 mmol) was added. The mixture stirred at -78 °C for 3 hours and then gradually warmed up to room temperature over night. Standard work up followed by chromatography (SiO<sub>2</sub>, ethyl acetate: hexanes = 1:4) to give 5.01g product (83%). The product was then dihydroxylated as described in Example 565, and treated with p-toluenesulfonic acid in benzene to give the lactone. Debenzylation via hydrogenation gave the desired amine.

MS (ESI): 561/563 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3479, 3311, 3056, 2942, 2853, 2726, 1777, 1654, 1574, 1556, 1503, 1408, 1354 cm<sup>-1</sup>.

#### Example 561

##### 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting 2-(4-hydroxypiperidin-4-yl)butyrolactone for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane,



which was made from a-(1-benzyl-4-hydroxy-4-piperidyl)-g-butarolactone (Salor) via hydrogenation.

MS (ESI): 562/564 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3484, 3289, 3054, 2928, 1768, 1644, 1575, 1464, 1358, 1264, 1138 cm<sup>-1</sup>.

#### Example 562

##### 4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-acetyl-4-hydroxypiperidine for 4-methoxypiperidine, which was prepared as follows: to a solution of ethyl vinyl ether (3.8 mL, 40 mmol) in THF, a solution of t-butyllithium (1.7 M, 24 mL, 40 mmol) was added at -78 °C. The reaction mixture was warmed up to 0 °C for about 30 min, and cooled down to -78 °C again before transferred to a slurry of CeCl<sub>3</sub> (10 g, 40 mmol) in THF at -78 °C. The mixture was stirred at -78 °C for about 1 hour, and a cold solution of N-benzyl-4-piperidinone (5.5 mL, 30 mmol) in THF was added. The reaction mixture was then gradually warmed up over night. Standard work up, followed by chromatography (SiO<sub>2</sub>, 1% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give 7.1 g product (91%). The product was then hydrolysed to ketone product in the presence of MeOH/THF/CH<sub>2</sub>Cl<sub>2</sub> (20:30:5) mixture solvents and HCl (3N, 7 mL) at 0 °C. The product was then deprotected via hydrogenation to give the final keto-amine.

MS (ESI): 519/521 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3486, 3312, 3210, 2950, 2923, 2859, 1706, 1604, 1580, 1558, 1508, 1352, 1242 cm<sup>-1</sup>.

#### Example 563

##### 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidiny)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 3-hydroxyazetidine for 4-methoxypiperidine, which was prepared from the N-diphenylmethyl-4-hydroxyaziridine (Maybridge) via hydrogenation.

MS (ESI): 449/451 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic):  $\nu_{\text{max}}$ : 3471, 3301, 3061, 1602, 1580, 1558, 1354  $\text{cm}^{-1}$ .

Example 564

4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except (1R,5S)-8-azabicyclo[3.2.1]octan-3-ol for 4-methoxypiperidine, which was prepared from tropanone as described by A.H. Newman, et al, J. Med. Chem. 1995, 38, 3933.

MS (ESI): 503/505 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic):  $\nu_{\text{max}}$ : 3480, 3317, 3204, 2918, 1706, 1603, 1580, 1558, 1352, 1243  $\text{cm}^{-1}$ .

Example 565

4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 567 as follows: to a solution of Example 567 (600 mg, 1.31 mmol) in THF/MeOH (55:5), NMO (460 mg, 3.93 mmol) was added followed by  $\text{OsO}_4$  (35 mg, 0.14 mmol). The reaction mixture was allowed to stir over night. Quenched with sodium thiosulfate. Standard work up, followed by chromatography ( $\text{SiO}_2$ , 10% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to give 260 mg (40%) of the title compound.

MS (ESI): 493/495 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic):  $\nu_{\text{max}}$ : 3478, 3296, 3082, 2924, 1641, 1604, 1581, 1554, 1513, 1354, 1227  $\text{cm}^{-1}$ .

Example 566 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting 3-(methylaminomethyl)pyridine (Maybridge) for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

MS (ESI): 499/501 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic): Vmax: 3475, 3300, 3151, 3061, 2928, 1682, 1555, 1484, 1395, 1352 cm<sup>-1</sup>.

Example 567

4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 1,2,3,6-tetrahydropyridine (Aldrich) for 4-methoxy piperidine.

MS (ESI): 459/461 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3473, 3305, 3090, 2928, 1670, 1578, 1558, 1508, 1355, 1244 cm<sup>-1</sup>.

Example 568

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting 4-(N-4'-methoxyphenylcarbamoyl)piperidine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane, which was prepared as described in Example 570 from N-benzyl-4-hydroxypiperidine.

MS (ESI): 459/461 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3473, 3305, 3090, 2928, 1649, 1581, 1560, 1508, 1355 cm<sup>-1</sup>.

Example 569

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 2-(4-hydroxypiperidin-4-yl)butyrolactone for 4-methoxypiperidine, which was made from α-(1-benzyl-4-hydroxy-4-piperidyl)-γ-butyrolactone (Salor) via hydrogenation.

MS (ESI): 561/563 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3462, 3392, 3297, 3256, 3108, 2948, 2859, 1765, 1638, 1598, 1579, 1556, 1505, 1355, 1240, 1158 cm<sup>-1</sup>.

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Example 570

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis(N-4'-methoxyphenylcarbamoyl)  
pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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Prepared as described for Example 370 except substituting 3R,4R-bis(N-4'-methoxyphenylcarbamoyl)pyrrolidine for 4-methoxypiperidine, which was made as follows: N-benzyl-3R,4R-dihydroxypyrrolidine (500 mg, 2.6 mmol) (Digital) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), 4-methoxyphenylisocyanate was added at room temperature. The reaction mixture was then allowed to stir for about 8 hours. White precipitate was collected, and washed with hexanes to give a pure product (1.23 g, 96%). The benzyl group was then deprotected via hydrogenation.  
MS (ESI): 777/779 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).  
IR (Mic): Vmax: 3481, 3302, 3194, 3057, 2955, 2838, 1726, 1604, 1555, 1514, 1415, 1228, 1076, 1030, 829 cm<sup>-1</sup>.

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Example 571

4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 370 except substituting (1S,5R)-8-azabicyclo[3.2.1]octan-3-ol for 4-methoxypiperidine, which was made from tropane (Aldrich) as described by A.H. Newman, et al. (J. Med. Chem. 1995, 38, 3933).  
MS (ESI): 503/505 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).  
IR (Mic): Vmax: 3472, 3303, 3157, 2939, 1681, 1600, 1580, 1554, 1354 cm<sup>-1</sup>.

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Example 572

4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

Prepared as described for Example 370 except substituting 3S,4S-dihydroxypyrrolidine for 4-methoxypiperidine which was prepared from the benzylprotected form (Digital) as described in Example 574.  
MS (ESI): 479/481 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

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IR (Mic): Vmax: 3484, 3299, 3193, 2928, 2854, 1629, 1584, 1561, 1536, 1513, 1435, 1078 cm<sup>-1</sup>.

Example 573

4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 367 except substituting 3R,4R-dihydroxypyrrolidine for "(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane" which was made as described in Example 574

MS (ESI): 480/482 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3484, 3302, 3209, 3077, 2932, 2724, 1628, 1599, 1585, 1562, 1514, 1433 cm<sup>-1</sup>.

Example 574

4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 3R,4R-dihydroxypyrrolidine for 4-methoxypiperidine and was prepared as follows: To a solution of N-benzyl-3R,4R-dihydroxypyrrolidine (Digital; 1.4 g, 7.25 mmol) in methanol,

Pd(OH)<sub>2</sub> on carbon (300 mg) was added followed by H<sub>2</sub> (1 atm.) at room temperature over night. Standard work up gave 635 mg of the product (85%).

MS (ESI): 479/481 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3484, 3303, 3208, 2932, 2861, 1585, 1562, 1538, 1513, 1434, 1078 cm<sup>-1</sup>.

Example 575

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (Acros) for 4-methoxypiperidine.

MS (ESI): 607/609 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic): Vmax: 3427, 3321, 3055, 1776, 1644, 1607, 1533, 1445, 1373, 1246  $\text{cm}^{-1}$ .

#### Example 576

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 586 as follows: to a solution of Example 586 (250 mg, 0.47 mmol) in  $\text{CH}_2\text{Cl}_2$  at 0 °C, mCPBA was added in small portion. The reaction was monitored by TLC. After reaction completion, quenched with sodium thiosulfate.

Standard work-up, followed by chromatography purification ( $\text{SiO}_2$ , 10% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to give 152 mg of the title compound (59%).

MS (ESI): 551/553 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic): Vmax: 3474, 3384, 3305, 3062, 2918, 1603, 1581, 1561, 1511, 1413, 1352, 1228  $\text{cm}^{-1}$ .

#### Example 577

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared from Example 586 as follows: to a solution of Example 586 (300 mg, 0.56 mmol) in acetic acid at 0 °C, a solution of  $\text{KMnO}_4$  in water was added till the color stayed.

Quenched with sodium thiosulfate. Standard work up, followed by chromatography separation ( $\text{SiO}_2$ , 5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to give 151 mg of the title compound (48%).

MS (ESI): 567/569 (M+H;  $^{79}\text{Br}/^{81}\text{Br}$ ).

IR (Mic): Vmax: 3475, 3348, 3210, 3061, 2955, 1694, 1585, 1308, 1235  $\text{cm}^{-1}$ .

#### Example 578

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one for 4-methoxypiperidine as follows: 1-phenyl-1,3,8-

5 triazaspiro[4,5]decaN-4-one (Acros: 350 mg, 1.5 mmol) was used to react with the  
chloride intermediate (200 mg, 0.48 mmol) in DMSO at 100 °C for over night. There  
were two major products, one of them was the desired compound (95 mg, 33%).

10 MS (ESI): 605/607 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

5 IR (Mic): Vmax: 3486, 3325, 3194, 3056, 2957, 2870, 1719, 1602, 1580, 1559, 1533,  
1353, 1256 cm<sup>-1</sup>.

15 Example 579

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)piperidinyl)-3-  
10 pyridazinyl)pyrido[2,3-d]pyrimidine

20 Prepared as described for Example 367 except substituting 4-(2-keto-1-  
benzimidazoliny)piperidine (Aldrich) for "(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane".

MS (ESI): 594/596 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

25 IR (Mic): Vmax: 3435, 3347, 3063, 1690, 1631, 1610, 1554, 1484, 1375 cm<sup>-1</sup>.

15 Example 580

4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-  
30 d]pyrimidine

20 Prepared from Ex. 328 as follows: to a solution of Example 328 (400 mg, 0.84  
mmol) in acetic acid, H<sub>2</sub>O<sub>2</sub> (30%) was added till all the starting material was converted to  
35 the desired product. Standard work up, followed by chromatography (SiO<sub>2</sub>, 10% MeOH  
in CH<sub>2</sub>Cl<sub>2</sub>) gave 301 mg of the title compound (72%).

MS (ESI): 495/497 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

40 IR (Mic): Vmax: 3440, 3060, 2869, 1695, 1645, 1606, 1484, 1372, 1243 cm<sup>-1</sup>.

25 MS (ESI): 495/497 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

Example 581

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)piperidinyl)-3-  
45 pyridyl)pyrido[2,3-d]pyrimidine

5

Prepared as described for Example 370 except substituting 4-(2-keto-1-benzimidazolyl)pyridine (Aldrich) for 4-methoxypiperidine.

MS (ESI): 593/595 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

10

IR (Mic): Vmax: 3473, 3304, 3063, 2918, 1603, 1581, 1512, 1413, 1353, 1228 cm<sup>-1</sup>.

5

Example 582

15

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 2-(2'-

20

10 methylaminoethyl)pyridine (Aldrich) for 4-methoxypiperidine:

MS (ESI): 512/514 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3475, 3303, 3046, 2931, 1648, 1583, 1561, 1519, 1405, 1354, 1142 cm<sup>-1</sup>.

25

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Example 583

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

30

Prepared as described for Example 370 except substituting 4-

(2' methylaminoethyl)pyridine (Aldrich) for 4-methoxypiperidine.

20 MS (ESI): 512/514 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

35

IR (Mic): Vmax: 3480, 3252, 3000, 1600, 1590, 1570, 1350 cm<sup>-1</sup>.

Example 584

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4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 370 except substituting 3-

(aminomethyl)pyridine (Aldrich) for 4-methoxypiperidine.

45

MS (ESI): 484/486 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3477, 3289, 3233, 3040, 1640, 1610, 1558, 1480, 1392, 1353, 1310,

30 1145 cm<sup>-1</sup>.

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Example 585

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4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

5 Prepared as described for Example 370 except substituting 2-(hydroxymethyl)piperidine (Aldrich) for 4-methoxypiperidine.

15

MS (ESI): 491/493 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3479, 3396, 3299, 3076, 2935, 2858, 1643, 1600, 1580, 1558, 1506, 1418, 1351 cm<sup>-1</sup>.

20

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Example 586

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

15 Prepared from Ex. 328 as follows: to a slurry of Example 328 (1.0 g, 2.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (220 mL), thioethanol (295 mL, 4.2 mmol) was added followed by BF<sub>3</sub> etherate (535 mL, 4.2 mmol). The mixture stirred at room temperature for 1 day, and quenched with NaHCO<sub>3</sub> (sat.). Standard work up, the crude product mixture was then recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/MeOH/hexanes to give the title compound (902 mg, 80%).

30

MS (ESI): 535/537 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

20 IR (Mic): Vmax: 3487, 3471, 3291, 3048, 2949, 2858, 1642, 1603, 1560, 1511, 1418, 1353, 1227, 1085 cm<sup>-1</sup>.

35

Example 587

40

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared as described for Example 370 except substituting 4-(4'-bromophenyl)-4-hydroxypiperidine (Aldrich) for 4-methoxypiperidine.

45

MS (ESI): 633/635 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3483, 3296, 3055, 2944, 1645, 1604, 1561, 1531, 1506, 1430, 1340, 1238 cm<sup>-1</sup>.

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Example 588

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridinyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

5

Prepared as described for Example 370 except substituting 1-(2'-pyridino)piperazine (Aldrich) for 4-methoxypiperidine.

15

MS (ESI): 539/541 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3476, 3289, 3052, 2929, 2843, 1642, 1597, 1559, 1481, 1398, 1231 cm<sup>-1</sup>.

10

20

Example 589

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethoxyethoxy)ethoxy)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

15

Prepared as described for Example 370 except substituting 1-(2-(2-hydroxyethoxy)ethyl)piperazine (Aldrich) for 4-methoxypiperidine..

MS (ESI): 550/552 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

30

IR (Mic): Vmax: 3490, 3396, 3279, 3143, 2919, 2852, 1633, 1604, 1582, 1555, 1504, 1424, 1337, 1241, 1119 cm<sup>-1</sup>.

20

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Example 590

4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethoxythio)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

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25

Prepared as described for Example 370 except substituting 4,4-di(2'-acetoxyethoxythio)piperidine for 4-methoxypiperidine. This amine was prepared as follows:

to a solution of 4-piperidinone hydrochloride salt (5.0 g, 32.6 mmol) in acetic acid (100 mL), 2-thioethoxythio-1-ol (3 mL, 42.8 mmol) was added followed by BF<sub>3</sub> etherate (9.0 mL, 71.0 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature for 3 days, and standard work-up gave a crude product 8.28 g (86%).

45

MS (ESI): 697/699 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

50

55

IR (Mic): Vmax 3482, 3300, 3058, 2944, 2853, 1738, 1602, 1574, 1560, 1508, 1352, 1231 cm<sup>-1</sup>.

Example 591

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 3-(methylaminomethyl)pyridine (Maybridge) for 4-methoxypiperidine.

MS (ESI): 498/500 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3477, 3298, 3092, 2923, 1645, 1604, 1559, 1516, 1399, 1356 cm<sup>-1</sup>.

Example 592

4-amino-5-(3-bromophenyl)-7-(6-(4-pyrrolidinylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared as described for Example 370 except substituting 4-(1-pyrrolidinyl)piperidine (Aldrich) for 4-methoxypiperidine

MS (ESI): 554/556 (M+H; <sup>79</sup>Br/<sup>81</sup>Br).

IR (Mic): Vmax: 3474, 3299, 3042, 2807, 1647, 1601, 1574, 1560, 1507, 1231 cm<sup>-1</sup>.

Example 593 4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

4-Amino-5-(3-bromophenyl)-7-(6-chloropyridaz-3-yl)pyrido[2,3-d]pyrimidine (165mg), prepared in Example 367, histamine (133mg), and potassium carbonate (166mg) were suspended in pyridine (2ml) and heated at 110°C for 20h. The reaction mixture was then directly chromatographed (TFA/MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound.

mp: δ 235°C; MS (ESI)<sup>+</sup> m/z: 488/490.

IR (cm<sup>-1</sup>): 3475, 3301, 3199, 1721, 1625, 1580, 1553, 1467, 1357, 1133.

Example 594

5

4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

10

Prepared by deformylation of Example 329 with hydrochloric acid in methanol and followed by treatment with iodoacetylnitrile in dimethylformamide.

5 IR (mic) 3473, 3299, 2822, 1561, 1234  $\text{cm}^{-1}$ ;

MS m/z 502 (M+H)<sup>+</sup>.

15

Example 595

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

10

20

Prepared as described for Example 370 except substituting 3-hydroxypyrrolidine for 4-methoxypiperidine.

IR (microscope) 3480, 3300, 1606, 1559, 1431, 1309  $\text{cm}^{-1}$ ;

25

MS m/z 463 (M+H)<sup>+</sup>.

15

Example 596

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

30

Prepared as described for Example 370 except substituting 3-methylpiperidine for 4-methoxypiperidine.

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IR (microscope) 3473, 3092, 1558, 1506, 1233  $\text{cm}^{-1}$ ;

MS m/z 476 (M+H)<sup>+</sup>.

40

Example 597

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine

25

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Prepared as described for Example 370 except substituting cis-3,5-dimethylmorpholine for 4-methoxypiperidine.

IR (microscope) 3475, 3090, 1561, 1508, 1239, 1175  $\text{cm}^{-1}$

30 MS m/z 492 (M+H)<sup>+</sup>.

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Example 598

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

5

Prepared as described for Example 370 except substituting 4,4-difluoropiperidine for 4-methoxypiperidine, 4,4-difluoropiperidine was prepared according to Tetrahedron, 1977, 33, 1707.

15

IR (microscope) 3474, 3091, 1507, 1237  $\text{cm}^{-1}$ ; MS  $m/z$  498 (M+H) $^{+}$ .

10

Example 599

20

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine

Prepared by the oxidation of Example 605 using  $\text{OsO}_4$  in  $\text{MeOH}/\text{CH}_2\text{Cl}_2/\text{acetone}$  (1:1:1) solution.

25

15 IR(KBr) 3470, 1600, 1564, 1316, 1287, 1122  $\text{cm}^{-1}$

MS  $m/z$  513 (M+H) $^{+}$ .

30

Example 600

4-amino-5-(3-bromophenyl)-7-(6-(thiazolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

20

Prepared according to the procedure of Example 306.

35

IR (microscope) 3468, 3052, 1557, 1509, 1407, 1289  $\text{cm}^{-1}$ ; MS  $m/z$  466 (M+H) $^{+}$ .

Example 601

40

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared according to the procedure of Example 306.

IR (microscope) 3466, 3090, 1563, 1508, 1234  $\text{cm}^{-1}$ ; MS  $m/z$  498 (M+H) $^{+}$ .

45

Example 602

30

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine

50

55

5

Prepared as described for Example 367 except substituting thiomorpholine for (1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane.

10

IR (microscope) 3426, 3063, 1605, 1556, 1442, 1377, 1265  $\text{cm}^{-1}$ ; MS  $m/z$  481 (M+H)<sup>+</sup>.

5

#### Example 603

4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydro-1H-pyrrolyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

15

Prepared according to the procedure of Example 306.

IR (microscope) 3468, 3060, 1607, 1550, 1443, 1265  $\text{cm}^{-1}$ ; MS  $m/z$  446 (M+H)<sup>+</sup>.

10

#### Example 604

20

4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

25

Prepared according to the procedure in Example 346, with potassium-*t*-butoxide and dibromomethane in dimethylformamide.

15

IR (microscope) 3468, 3052, 1557, 1509, 1407, 1289  $\text{cm}^{-1}$ ; MS  $m/z$  520 (M+H)<sup>+</sup>.

30

#### Example 605

4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine

35

Prepared according to the procedure of Example 246c substituting thiomorpholine for dimethylamine.

IR(KBr) 3487, 1601, 1562, 1502, 1128  $\text{cm}^{-1}$

MS  $m/z$  481 (M+H)<sup>+</sup>

40

#### Example 606

25

4-amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

45

The procedure of Example 392 was followed, except substituting 5-acetyl-2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridine for 5-acetyl-2-morpholinylpyridine. Treatment with HCl/ethanol to form the hydrochloride salt was omitted, and the free base was obtained instead.

50

55

IR (MIC) 3480, 3120, 1635, 1605, 1561, 1515, 1429, 1240 cm<sup>-1</sup>; MS m/z 507 (M-H)<sup>+</sup>

Example 607

4-amino-5-isopropyl-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine

Prepared by the method of Example 327, substituting 2-methylpropanal for 3-bromobenzaldehyde.

mp: ~ 205°C;

MS (FAB)<sup>+</sup> m/z calc'd for C<sub>22</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>: 407.2195, found: 407.2186.

IR (cm<sup>-1</sup>): 3318, 3142, 2960, 1586, 1554, 1514, 1425, 1344, 1240, 1105.

Example 608.3

4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared as described for Example 370 substituting

piperidine for 4-methoxypiperidine, followed by treatment with 1M HCl ether

MS (APCI<sup>+</sup>) m/z 461 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.05 (bs, 1H), 9.00 (m, 1H), 8.90 (s, 1H), 8.70 (m, 1H), 8.23 (m, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.40 (m, 2H), 3.87 (m, 4H), 1.68 (m, 6H)

Example 609

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxvimino)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine

The title compound was prepared as described for Example 370 substituting 3-(4'-tetrahydropyranyl-oximinyl)pyrrolidine (prepared as in A-321236.3) for 4-

methoxypiperidine, followed by treatment with 1M HCl ether.

MS (ESI<sup>+</sup>) m/z 560 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.00 (bs, 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.65 (m, 1H), 7.97 (s, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.38 (m, 1H), 7.04 (m, 1H), 4.39 (m, 2H), 4.25 (m, 1H), 3.84 (m, 4H), 3.42 (m, 2H), 2.94 (m, 2H), 1.94 (m, 2H), 1.57 (m, 2H)

5

Example 610 4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

10

Prepared as described for Example 395 except substituting 2-trifluoromethylbenzaldehyde for 2,5-dichlorobenzaldehyde.

5 IR (KBr) 3495, 1674, 1634, 1487, 1421, 1321, 1302, 1190cm<sup>-1</sup>;  
MS m/z 452.9 (M+H)<sup>+</sup>.

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## Claims

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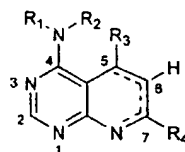
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## WHAT IS CLAIMED IS:

1. A method of inhibiting adenosine kinase by administering to a mammal in need of such treatment a pharmaceutically effective amount of one or more compounds of formula I



I.

or a pharmaceutically acceptable salt or amide thereof in vitro or to a mammal wherein,

$R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclecarbonyl, hydroxyalkyl, iminoalkyl, and  $(NZ_1Z_2)$ alkyl, or  $R^1$  and  $R^2$  may join together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl,  $(NZ_1Z_2)$ alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

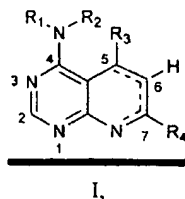
$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl;

$R^E$  is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

with the proviso that the following compounds are excluded,

- 4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,
- 4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,
- 4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,
- 4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,
- 4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,
- 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine, and
- 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

2. A method of inhibiting adenosine kinase according to claim 1 comprising administering a compound of formula I



5 or a pharmaceutically acceptable salt or amide thereof wherein,

10  $R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and  $(NZ_1Z_2)$ alkyl, or  $R^1$  and  $R^2$  may join  
15 together with the nitrogen atom to which they are attached to form a 6 membered ring optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

20  $R^3$  is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl,  $(NZ_1Z_2)$ alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting of aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

25  $R^4$  is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl and heterocycle;

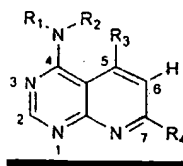
30  $R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl;

20  $R^E$  is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl;

40  $Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxyalkyl, alkyl, alkylcarbonyl, benzyl, benzyloxyalkyl, and formyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained.

45 3. A method of inhibiting adenosine kinase according to claim 1 comprising  
30 administering a compound of formula II



II,

or a pharmaceutically acceptable salt or amide thereof wherein,

$R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and  $(NZ_1Z_2)$ alkyl, or  $R^1$  and  $R^2$  may join together with the nitrogen atom to which they are attached to form a 6 membered ring optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

$R^3$  is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl,  $(NZ_1Z_2)$ alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting of aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

$R^4$  is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl and heterocycle;

$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl;

$R^E$  is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl; and,

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl.

4. The method according to claim 3 wherein R<sup>4</sup> is selected from the group consisting of:

phenyl; thiophene-2-yl; 3-methyl-2-oxobenzoxazolin-6-yl; 2-(dimethylamino)-5-pyrimidinyl; 2-(N-formyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methylamino)-5-pyrimidinyl; 2-(1-morpholinyl)-5-pyrimidinyl; 2-(1-pyrrolidinyl)-5-pyrimidinyl; 2-dimethylamino-5-pyrimidinyl; 2-furanyl; 2-oxobenzoxazolin-6-yl; 2-pyridyl; 3-(dimethylamino)phenyl; 3-amino-4-methoxyphenyl; 3-bromo-4-(dimethylamino)phenyl; 3-methoxyphenyl; 3-methyl-4-(N-acetyl-N-methylamino)phenyl; 3-methyl-4-(N-formyl-N-methylamino)phenyl; 3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl; 3-methyl-4-(N-methylamino)phenyl; 3-methyl-4-pyrrolidinylphenyl; 3-pyridyl; 3,4-dichlorophenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 4-(acetylamino)phenyl; 4-(dimethylamino)-3-fluorophenyl; 4-(dimethylamino)phenyl; 4-(imidazol-1-yl)phenyl; 4-(methylthio)phenyl; 4-(morpholinyl)phenyl; 4-(N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-(2-methoxyethyl)amino)phenyl; 4-(N-acetyl-N-methylamino)phenyl; 4-(N-ethyl-N-formylamino)phenyl; 4-(N-ethylamino)phenyl; 4-(N-formyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-isopropylamino)phenyl; 4-(N-methyl-N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl; 4-(N-methyl-N-(2-cyano)ethylamino)phenyl; 4-(N-methyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-methyl-N-(3-methoxy)propionylamino)phenyl; 4-(N-methyl-N-acetylamino)phenyl; 4-(N-methyl-N-formylamino)phenyl; 4-(N-methyl-N-trifluoroacetylamino)phenyl; 4-(N-morpholinyl)phenyl; 4-(thiophene-2-yl)phenyl; 4-(urcideo)phenyl; 4-(2-(dimethylamino)acetylamino)phenyl; 4-(2-methoxy)acetylamino)ethyl)amino)phenyl; 4-(2-methoxy)ethoxyphenyl; 4-(2-oxo-3-oxazolidinyl)phenyl; 4-(4-methoxy-2-butyl)phenyl; 4-(4-methylpiperidinyl)phenyl; 4-(5-pyrimidinyl)phenyl; 4-aminophenyl; 4-bromophenyl; 4-butoxyphenyl; 4-carboxamidophenyl; 4-chlorophenyl; 4-cyanophenyl; 4-diethylaminophenyl; 4-diethylmalonylallylphenyl; 4-dimethylaminophenyl; 4-ethoxyphenyl; 4-ethylphenyl; 4-fluorophenyl; 4-hydroxyphenyl; 4-imidazolylphenyl; 4-

5 iodophenyl; 4-isopropylphenyl; 4-methoxyphenyl; 4-methylaminophenyl; 4-methylsulfonylphenyl; 4-morpholinylphenyl; 4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl; 4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl; 4-N-ethyl-  
10 N-(2-methoxyethyl)amino)phenyl; 4-N-formylpiperazinylphenyl) 4-nitrophenyl; 4-piperidinylphenyl; 4-(3-pyridyl)phenyl; 4-pyrrolidinylphenyl; 4-t-butylacrylphenyl; 5-(dimethylamino)thiophene-2-yl; 5-amino-2-pyridyl; 5-dimethylamino-2-pyrazinyl; 3-dimethylaminopyridazin-6-yl; 5-dimethylamino-2-pyridyl; 5-pyrimidinylphenyl; 6-(N-methyl-N-formylamino)-3-pyridinyl; 6-(N-methyl-N-methoxyethylamino)-3-pyridinyl; 6-(2-oxo-3-oxazolidinyl)-3-pyridinyl; 6-dimethylamino-3-pyridinyl; 6-imidazolyl-3-  
15 pyridinyl; 6-morpholinyl-3-pyridinyl; 6-pyrrolidinyl-3-pyridinyl; 6-(2-propyl)-3-pyridinyl; 6-(4-formylamino)phenyl; 6-(4-oxopiperidinyl)-3-pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl; 6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazinyl; 6-(4-methoxyiminopiperidinyl)-3-pyridazinyl; 6-phenylmethoxy-3-  
20 pyridazinyl; 6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl; 6-(1,3-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl; 6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl; 6-(N-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide; 2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl; 5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl; 2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-(4-methoxypiperidinyl)-3-pyridyl; 6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl; 6-isopropoxy-3-pyridazinyl; 6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranyloxy)-3-pyridazinyl; 6-morpholinylethoxy-3-pyridazinyl; 6-(4-ethoxypiperidinyl)-3-pyridazinyl; 6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl; 6-(3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl;

5 6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl; 6-(3-(R)-  
tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(3-(S)-  
10 tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-  
hydroxypyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxypyrrolidinyl)-3-  
5 pyridazinyl; 6-(trans-3-ethoxy-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(trans-3,4-bis-  
ethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3,4-bis-ethoxypyrrolidinyl)-3-pyridyl; 6-(cis-  
15 3,4-bis-ethoxypyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxypyrrolidinyl)-3-pyridazinyl;  
6-(cis-3-ethoxy-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(cis-3-amino-4-  
hydroxypyrrolidinyl)-3-pyridazinyl; 6-(cis-3-amino-4-hydroxypyrrolidinyl)-3-pyridyl; 6-  
20 (1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(4-tertbutyl)piperidinyl-3-  
pyridazinyl; 6-(4-N-formyl)piperidinyl-3-pyridazinyl; 6-morpholinyl-3-pyridazinyl; 4-N-  
1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide; 4-(4-dioxo-8-  
25 azaspiro[4.5]decan-8-ylcarboxamide)phenyl; 6-(3-methoxy-1,5-dioxo-9-  
azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(1,5-dioxo-3-hydroxymethyl-9-  
15 azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-  
pyridazinyl; 6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2R,3R)-  
2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2S,3S)-  
30 2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-(4,4-(cis-1,2-  
dioxycyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1S,2S-  
20 dimethoxymethylethanedioxy)piperidinyl)-3-pyridazinyl; 6-(4,4-(cis-3,4-dioxy-  
oxacyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-  
35 methoxypropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-  
hydroxymethylpropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(2-(2,2-spiro-  
oxacyclopropane-1,3-dioxypropylene)piperidinyl)-3-pyridazinyl; 6-morpholinyl-3-  
40 pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridyl; 6-(4-(N-  
methylpiperazinyl)iminopiperidinyl)-3-pyridyl; 6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-  
3-pyridyl; 6-(4-ethylpiperidinylcarboxylate)-3-pyridyl; 2-phenylmethyl-3(2H)-  
45 pyridazinone-6-yl; 6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-  
morpholinylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N,N-  
30 dimethylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methyl-N-



5 methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxypiperidinyl)-3-pyridyl; 6-(4-N-acetyl-piperazinyl)-3-pyridyl; 6-(4-cyanopiperidinyl)-3-pyridyl; 6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl; 4-morpholinylbenzenesulfonamide; 4-N-4,4-ethylenedioxypiperidinylbenzenesulfonamide; 4-N-cyclopropylbenzenesulfonamide; 4-piperidinebenzenesulfonamide; 4-(4-cyanopiperidine)benzenesulfonamide; 4-N-cyclopropylmethylbenzenesulfonamide; 4-N,N-dimethylaminobenzenesulfonamide; 4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide; 4-(4-hydroxypiperidine)benzenesulfonamide; 4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide; 3-fluoro-4-thiomorpholinylphenyl; 6-(thiomorpholinyl)-3-pyridyl; 6-(4,4-dioxothiomorpholinyl)-3-pyridyl; 4-(4,4-ethylenedioxypiperidinylcarboxamide)phenyl; 4-(N-cyclopropylcarboxamide)phenyl; 4-(morpholinylcarboxamide)phenyl; 6-N-cyclopropylamino-3-pyridyl; 4-(4-hydroxypiperidinylcarboxamide)phenyl; 6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl; 6-hexahydropyrimidine-3-pyridyl; 6-(S)-2-ethoxyethoxypyrrolidinyl-3-pyridyl; 6-(R)-2-ethoxyethoxypyrrolidinyl-3-pyridyl; 6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-[(3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-2-one-5-yl]-3-pyridyl; 6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl; 6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane-3-pyridyl; 6-(2-imidizolidone-1-yl)-3-pyridyl; 4-(2,4-(1H,3H)-quinazolin-3-yl)phenyl; 6-morpholinylcarboxamide-3-pyridazinyl; 6-methoxy-3-pyridazinyl; 6-N,N-diethoxyethylamino-3-pyridazinyl; 6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranylmethyl)piperidinyl)-3-pyridazinyl; 6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl; 6-N-methyl-N-1,3-dioxalanemethylamino-3-pyridazinyl; 6-(4,4-dioxyethylenecyclohexyloxy)-3-pyridazinyl; 6-dihydroxymethylmethoxy-3-pyridazinyl; 6-(3-pyridyloxy)-3-pyridazinyl; 4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl; 6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl; 6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-

5 methylpyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-  
(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(cis-3-hydroxy-4-  
10 methylpyrrolidinyl)-3-pyridyl; 6-(trans-3-cyano-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(3-  
hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl; 6-(S-2-(4-  
5 tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl; 6-(2-(4-  
tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl; 2-morpholinyl-5-thiazoyl; 5-  
15 bromo-2-thienyl; 2,5-dimethyl-3-thienyl; 5-chloro-2-thienyl; 2,4-dimethyl-5-thiazoyl; 5-  
methyl-2-thienyl; 2-furanyl; 2-(4,4-dioxyethylenepiperidinyl)-5-thiazoyl; 3-thienyl; 3-  
methyl-2-thienyl; 2-morpholinyl-4-thiazoyl; 2-morpholinyl-4-trifluoromethyl-5-thiazoyl;  
10 5-morpholinyl-2-thienyl; 4-methyl-2-morpholinyl-5-thiazoyl; 2,5-dichloro-3-thienyl; 2,5-  
20 dimethyl-3-furanyl; N-methyl-2-pyrrolyl; 2-N,N-dimethylamino-5-thiazoyl; 2-  
morpholinyl-5-thiazoyl; 2-(4,4-dioxythiomorpholinyl)-5-thiazoyl; 1-N-methyl-2-  
morpholinyl-5-imidazolyl; 2-morpholinyl-5-oxazolyl; 2-N-methyl-N-methoxyethylamino-  
5-thiazoyl; 2-N-methyl-N-ethylamino-5-thiazoyl; 2-N-pyrrolidinyl-5-thiazoyl; 2-N-  
15 methyl-N-propylamino-5-thiazoyl; 2-N,N-diethylamino-5-thiazoyl; 2-(N-  
methypiperazinyl)-5-thiazoyl; 2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl; 2-N-methyl-N-(2-  
pyridylethyl)-5-thiazoyl; 2-(4-oxopiperazinyl)-5-thiazoyl; 2-(4-(N-  
30 morpholinyl)iminopiperazinyl)-5-thiazoyl; 6-N-morpholine-3-pyridinesulfonamide; 2-(4-  
oxopiperidinyl)-5-pyrimidyl; 2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl; 5-(4,4-  
20 dioxethylenepiperidinyl)-2-pyrazinyl; 5-(4-oxopiperidinyl)-2-pyrazinyl; 6-N-cyclopropyl-  
3-pyridinesulfonamide; 6-N-(4,4-dioxethylenepiperidinyl)-3-pyridinesulfonamide; 2-(4-  
35 (4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl; 6-(4-  
(phenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(tert-butyloxy)iminopiperidinyl)-3-  
pyridyl; 6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxyiminopiperidinyl)-  
40 3-pyridyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-  
methoxyethoxyiminopiperidinyl)-3-pyridyl; 6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-  
pyridyl; 6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl; 6-(4-(1-(4-  
45 tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(4'-acetyl-  
4'-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(1-(isopropylcaboxymethoxy)iminoethyl))-4-  
30 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethylcaboxymethoxy)iminoethyl))-4-

5 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(methoxycarbonylmethoxy)iminoethyl))-4-  
hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-  
10 hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-  
pyridyl; 6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-  
5 (methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(hydroxy)iminoethyl))-4-  
hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl;  
15 6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(1-(4-  
tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(3-  
butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-butyrolactone)-4-  
20 hydroxypiperidinyl)-3-pyridazinyl; 6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl; 6-(3-  
hydroxyazetidyl)-3-pyridyl; 6-(cis-3-hydroxytropanyl)-3-pyridyl; 6-(cis-2,3-  
dihydroxypiperidinyl)-3-pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl;  
25 6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl; 6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-  
3-pyridazinyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(trans-3,4-bis(N-  
15 4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl; 6-(trans-3-hydroxytropanyl)-3-  
pyridyl; 6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-(R,R-trans-3,4-  
dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl;  
30 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl); 6-(8-(1-phenyl-1,3,8-  
triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl); 6-(4-(2-keto-1-benzimidazolyl)piperidinyl)-  
20 3-pyridazinyl; 6-(4-oxothiomorpholinyl)-3-pyridyl; 6-(4-(2-keto-1-  
benzimidazolyl)piperidinyl)-3-pyridyl; 6-(N-methyl-N-(2-pyridylethyl)amino)-3-  
35 pyridyl; 6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl; 6-N-(3-pyridylmethyl)amino-3-  
pyridyl; 6-(2-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(4-  
bromophenyl)piperidinyl)-3-pyridyl; 6-(4-N-(2-pyridyl)piperazinyl)-3-pyridyl; 6-(4-N-  
40 (2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl; 6-(4,4-diacetoxyethylthio)piperidinyl)-3-  
pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridyl; 6-(4-pyrrolidinylpiperidinyl)-  
3-pyridyl; 6-(4-N-cyanomethylpiperazinyl)-3-pyridyl; 6-(3-hydroxypyrrolidinyl)-3-pyridyl;  
45 6-(4-methylpiperidinyl)-3-pyridyl; 6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl; 6-(4,4-  
difluoropiperidinyl)-3-pyridyl; 6-(4,4-dioxythiomorpholinyl)-3-pyridazinyl; 6-  
30 thiazolidinyl)-3-pyridyl; 6-(1,1-dioxythiazolidinyl)-3-pyridyl; 6-thiomorpholinyl)-3-

pyridazinyl; 6-(2,5-dihydropyrrolyl)-3-pyridyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-hydroxy-3-pyridazinyl; 6-piperidinyl-3-pyridyl; and 6-(4-tetrahydropyraniloxy)iminopyrrolidinyl-3-pyridyl; 6-morpholinyl-3-pyridyl.

5 5. The method according to claim 3 wherein R<sup>3</sup> is selected from the group consisting of:

(thiophene-2-yl)methyl; (thiophene-3-yl)methyl; butyl; cycloheptyl; pentyl; thiophene-2-yl; 1-(3-bromophenyl)ethyl; 2-(N-phenylmethoxycarbonyl)aminophenyl; 2-(3-bromophenyl)ethyl; 2-(3-cyanophenyl)methyl; 2-(4-bromophenyl)ethyl; 2-(5-chloro-2-(thiophen-3-yl)phenyl); 2-bromophenyl; 2-furanyl; 2-methylpropyl; 2-phenylethyl; phenylmethyl; 2,3-dimethoxyphenyl; 2,3-methylenedioxyphenyl; 3-(furan-2-yl)phenyl; 3-(thiophen-2-yl)phenyl; 3-(2-pyridyl)phenyl; 3-(3-methoxybenzyl)phenyl; 2-(3-aminopropenyl)phenylmethyl; 3-benzoyloxyphenyl; 3-bromo-4-fluorophenyl; 3-bromo-5-iodophenyl; 3-bromo-5-methoxyphenyl; 3-bromophenyl; 3-bromophenyl)methyl; 3-carboxamidophenyl; 3-chlorophenyl; 3-cyanophenyl; 3-diethylmalonylallylphenyl; 3-dimethylaminophenyl; 3-ethoxyphenyl; 3-fluoro-5-trifluoromethylphenyl; 3-fluorophenyl; 3-hydroxyphenyl; 3-iodophenyl; 3-methoxyethoxyphenyl; 3-methoxyphenyl; 3-methylphenyl; 3-methylsulfonylphenyl; 3-methylthiophenyl; 3-t-butylacrylphenyl; 3-trifluoromethoxyphenyl; 3-trifluoromethylphenyl; 3-vinylpyridinylphenyl; 3,4-dichlorophenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 3,5-di(trifluoromethyl)phenyl; 3,5-dibromophenyl; 3,5-dichlorophenyl; 3,5-dimethoxyphenyl; 3,5-dimethylphenyl; 4-(2-propyl)phenyl; 4-(2-propyl)oxyphenyl; 4-benzoyloxyphenyl; 4-bromophenyl; 4-bromothiophene-2-yl; 4-butoxyphenyl; 4-dimethylaminophenyl; 4-fluoro-3-trifluoromethylphenyl; 4-methoxyphenyl; 4-neopentylphenyl; 4-phenoxyphenyl; 5-bromothiophene-2-yl; 5-cyclohexyl; 5-cyclopropyl; 5-hexyl; 5-methyl; 5-phenyl; (2-bromo-5-chlorophenyl)methyl; (2-bromophenyl)methyl; (5-chloro-2-(3-methoxyphenyl)phenyl)methyl; 3-bromophenyl; 2-pyridyl; 2-ethoxyphenyl; 5-ethoxyphenyl; 2,5-dichlorophenyl; 2,5-dimethylphenyl; 3-fluorophenyl; 3-trifluoromethylphenyl; 5-trifluoromethylphenyl; 3,5-dichlorophenyl; 4-bromo-2-thienyl; 3-bromo-2-thienyl; 3-cyanophenyl; 4-tetrahydropyranyl; 3-indolyl; 5-indolyl; 4-quinolyl;

2-bromophenyl; 4-fluorophenyl; 4,4-difluorocyclohexyl; 1,1-dimethyl-3-butenyl; 2,3-dichlorophenyl; isopropyl; and 2-trifluorophenylphenyl.

6. The method according to claim 1 wherein the compound is selected from the group consisting of:

4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-(2-propyl)phenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-butyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-(2-propyl)oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-benzyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

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20 4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-(2-propyl)phenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-(2-propyl)phenyl)-7-(4-t-butylacetylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-benzyloxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-phenylpyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,4-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyethoxyphenyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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30 4-amino-5-(5-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(acetylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-

5 d]pyrimidine;

4-(4-fluorophenyl)amino)-5-(3-bromophenyl)-7-(4-

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dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-

d]pyrimidine;

10 4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-

d]pyrimidine;

4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

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d]pyrimidine;

15 4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

d]pyrimidine;

4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

20 d]pyrimidine;

4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-

d]pyrimidine;

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-

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25 d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4,4-bis(acetyl amino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropyl-amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-(N-phenylmethoxycarbonyl)aminoethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenylmethyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclopropyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-methyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-acetylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-formylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-(methoxyacetyl)amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-trifluoroacetyl amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-pentanoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-benzoylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-(N-BOC-glycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-(N-phthalimidylglycyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-(ethoxycarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-(ethylaminocarbonyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-allylamino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine;

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4-(2-(N,N-dimethylamino)ethylamino)-5-(4-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine;

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4-(4-(N,N-dimethylamino)butylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl) pyrido[2,3-d]pyrimidine;

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4-(N-allyl-N-formylamino)-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

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4-diacetyl amino-5-(p-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-((thiophene-2-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((thiophene-3-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-

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methoxy)acetyl amino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)acetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-

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diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-

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pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-

d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-

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pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-

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pyrido[2,3-d]pyrimidine;

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4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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15 4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)-phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

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4-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride;

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4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(3-(methoxypropynyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(4-(2-(dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-1-(N-methylamino)ethyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(1-(dimethylamino)-1-methylethyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-diethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-(N-methyl-N-formyl)amino)-  
phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-((N-(benzyloxycarbonyl)-4-piperidiny)methyl)-7-(6-morpholinyl-3-  
pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-  
pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl))amino)-3-  
pyridazinyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-acetylpiperazinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-cyclohexyl-7-(6-2-(N,N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-cyclohexyl-7-(6-azetidiny-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-cyclohexyl-7-(6-(2-methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine;

35

4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25

4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(N-oxiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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d]pyrimidine;

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5

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine.

10

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl-N-oxide)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt;

20

4-amino-5-(3-bromophenyl)-7-(4-methylenylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-cyclohexyl-7-(6-(4-methylenylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine;

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- 5 4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 10 4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 5 4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 15 4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 10 (S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 20 (S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazolyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyiminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranlyoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranlyoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/24901

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1 to 6, 8-9  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1 to 6, 8 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.  
PCT/US 99/24901

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2,3-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25

4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3,

20

d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40

25

4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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5

4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxo-11-azadispiro[4.2.5.2]pentadecan-11-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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10 4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-dioxo-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

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20 4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(6-(hexahydropyrimidine)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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15 4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxalanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-

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pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-

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pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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- 5 4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;
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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxythiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazolyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-(2-pyridylethyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N-morpholino-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyll)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidinyll)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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- 5 4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 50 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 55 4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny) piperidinyl)-3-pyridaziny)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny) piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethyl) piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl) piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridyl) piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethoxyethyl) piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethylthio) piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-pyrrolidinyl) piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridaziny)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-pyridaziny)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridaziny)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydropyrrolyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridaziny)pyrido[2,3-d]pyrimidine;  
amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25

4-amino-5-isopropyl-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxyimino)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine; and

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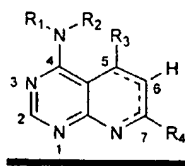
4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

8. A method of treating ischemia, neurological disorders, nociception, inflammation, immunosuppression, gastrointestinal disfunctions, diabetes and sepsis in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1 or 3.

9. A method according to Claim 8 wherein the method consists of treating cerebral ischemia, myocardial ischemia, angina, coronary artery bypass graft surgery, percutaneous transluminal angioplasty, stroke, thrombotic and embolic conditions, epilepsy, anxiety, schizophrenia, pain perception, neuropathic pain, visceral pain, arthritis, sepsis, diabetes and abnormal gastrointestinal motility.

10. A compound of formula I



I,

or a pharmaceutically acceptable salt or amide thereof wherein,

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocycle, heterocyclealkyl, heterocyclecarbonyl, hydroxyalkyl, iminoalkyl, and (NZ, Z<sub>2</sub>)alkyl, or R<sup>1</sup> and R<sup>2</sup> may join

5 together with the nitrogen atom to which they are attached to form a 5-7 membered ring optionally containing 1-2 additional heteroatoms selected from the group consisting of O, N, and S;

10  $Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, 5 alkoxy carbonyl, alkyl, alkyl carbonyl, benzyl, benzyloxy carbonyl, and formyl;

$R^1$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, 15 cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ, $Z_2$ )alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting aryl and arylalkyl;

20  $R^B$  is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and 15 heterocyclealkyl;

$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, 25 cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

$R^C$  is selected from aryl, arylalkyl, heterocycle, and heterocyclealkyl;

15  $R^D$  is selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, 25 heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, 30 and heterocyclesulfonyl;

$R^E$  is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, 20 heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, 35 heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

40 25 with the proviso that the following compounds are excluded,

4-amino-5-(4-chlorophenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-methoxyphenyl)-7-(4-nitrophenyl)pyridol[2,3-d]pyrimidine,

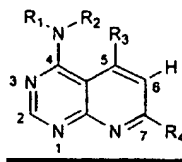
45 4-amino-5-(4-fluorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

4-amino-5-(4-chlorophenyl)-7-(4-fluorophenyl)pyridol[2,3-d]pyrimidine,

30 4-amino-5-phenyl-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,

4-amino-5-phenyl-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine,  
 4-amino-5-(4-methoxyphenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine,  
 4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine, and  
 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidine.

11. A compound according to claim 10 of formula II



II,

or a pharmaceutically acceptable salt or amide thereof wherein,

$R^1$  and  $R^2$  are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aminocarbonyl, aryl, arylcarbonyl, carboxyalkyl, formyl, haloalkylcarbonyl, heterocyclealkyl, hydroxyalkyl, iminoalkyl, and  $(NZ, Z_2)$ alkyl, or  $R^1$  and  $R^2$  may join together with the nitrogen atom to which they are attached to form a 6 membered ring optionally containing 1 additional heteroatom selected from the group consisting of O, N, and S;

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

$R^3$  is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocyclealkyl,  $(NZ, Z_2)$ alkyl, and  $-R^A R^B$ ;

$R^A$  is selected from the group consisting of aryl and arylalkyl;

$R^B$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, and heterocycle;

$R^4$  is selected from the group consisting of alkoxyalkynyl, alkynyl, aryl, heterocycle, and  $-R^C R^D R^E$ ;

$R^C$  is selected from the group consisting of aryl and heterocycle;

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$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleoxy, and heterocyclesulfonyl; and

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$R^E$  is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, and heterocycleoxyiminoalkyl.

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12. A compound according to claim 10 wherein  $R^4$  is selected from the group consisting of:

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phenyl; thiophene-2-yl; 3-methyl-2-oxobenzoxazolin-6-yl; 2-(dimethylamino)-5-pyrimidinyl; 2-(N-formyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl; 2-(N-methylamino)-5-pyrimidinyl; 2-(1-morpholinyl)-5-pyrimidinyl; 2-(1-pyrrolidinyl)-5-pyrimidinyl; 2-dimethylamino-5-pyrimidinyl; 2-furanyl; 2-oxobenzoxazolin-6-yl; 2-pyridyl; 3-(dimethylamino)phenyl; 3-amino-4-methoxyphenyl; 3-bromo-4-(dimethylamino)phenyl; 3-methoxyphenyl; 3-methyl-4-(N-acetyl-N-methylamino)phenyl; 3-methyl-4-(N-formyl-N-methylamino)phenyl; 3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl; 3-methyl-4-(N-methylamino)phenyl; 3-methyl-4-pyrrolidinylphenyl; 3-pyridyl; 3,4-dichlorophenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 4-(acetylamino)phenyl; 4-(dimethylamino)-3-fluorophenyl; 4-(dimethylamino)phenyl; 4-(imidazol-1-yl)phenyl; 4-(methylthio)phenyl; 4-(morpholinyl)phenyl; 4-(N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-(2-methoxyethyl)amino)phenyl; 4-(N-acetyl-N-methylamino)phenyl; 4-(N-ethyl-N-formylamino)phenyl; 4-(N-ethylamino)phenyl; 4-(N-formyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-isopropylamino)phenyl; 4-(N-methyl-N-(2-(dimethylamino)ethyl)amino)phenyl; 4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl; 4-(N-methyl-N-(2-cyano)ethylamino)phenyl; 4-(N-methyl-N-(2-methoxyethyl)amino)phenyl; 4-(N-methyl-N-(3-methoxy)propionylamino)phenyl; 4-(N-methyl-N-acetylamino)phenyl; 4-(N-methyl-N-formylamino)phenyl; 4-(N-methyl-N-trifluoroacetylamino)phenyl; 4-(N-

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morpholinyl)phenyl; 4-(thiophene-2-yl)phenyl; 4-(ureido)phenyl; 4-(2-  
 (dimethylamino)acetilamino)phenyl; 4-(2-methoxy)acetilaminoethylamino)phenyl; 4-  
 (2-methoxy)ethoxyphenyl; 4-(2-oxo-3-oxazolidinyl)phenyl; 4-(4-methoxy-2-butyl)phenyl;  
 4-(4-methylpiperidinyl)phenyl; 4-(5-pyrimidinyl)phenyl; 4-aminophenyl; 4-bromophenyl;  
 4-butoxyphenyl; 4-carboxamidophenyl; 4-chlorophenyl; 4-cyanophenyl; 4-  
 diethylaminophenyl; 4-diethylmalonylallylphenyl; 4-dimethylaminophenyl; 4-  
 ethoxyphenyl; 4-ethylphenyl; 4-fluorophenyl; 4-hydroxyphenyl; 4-imidazolylphenyl; 4-  
 iodophenyl; 4-isopropylphenyl; 4-methoxyphenyl; 4-methylaminophenyl; 4-  
 methylsulfonylphenyl; 4-morpholinylphenyl; 4-N-(2-(dimethylamino)ethyl)-N-  
 formylamino)phenyl; 4-N-(3-methoxypropionyl)-N-isopropylamino)phenyl; 4-N-ethyl-  
 N-(2-methoxyethyl)amino)phenyl; 4-N-formylpiperazinylphenyl; 4-nitrophenyl; 4-  
 piperidinylphenyl; 4-(3-pyridyl)phenyl; 4-pyrrolidinylphenyl; 4-t-butylacrylphenyl; 5-  
 (dimethylamino)thiophene-2-yl; 5-amino-2-pyridyl; 5-dimethylamino-2-pyrazinyl; 3-  
 dimethylaminopyridazin-6-yl; 5-dimethylamino-2-pyridyl; 5-pyrimidinylphenyl; 6-(N-  
 methyl-N-formylamino)-3-pyridinyl; 6-(N-methyl-N-methoxyethylamino)-3-pyridinyl; 6-  
 (2-oxo-3-oxazolidinyl)-3-pyridinyl; 6-dimethylamino-3-pyridinyl; 6-imidazolyl-3-  
 pyridinyl; 6-morpholinyl-3-pyridinyl; 6-pyrrolidinyl-3-pyridinyl; 6-(2-propyl)-3-pyridinyl;  
 (4-formylamino)phenyl; 6-(4-oxopiperidinyl)-3-pyridazinyl; 6-(4-  
 morpholinyliminopiperidinyl)-3-pyridazinyl; 6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-  
 5-yl)-3-pyridazinyl; 6-(4-methoxyiminopiperidinyl)-3-pyridazinyl; 6-phenylmethoxy-3-  
 pyridazinyl; 6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl; 6-(1,3-dioxa-8-  
 azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl;  
 6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl; 6-(1-oxa-4,4-dioxido-4-thia-8-  
 azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-  
 pyridyl; 6-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-  
 triazaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-  
 yl)-3-pyridyl; 6-(N-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide; 2-(1,1-  
 dioxidothiomorpholinyl)-5-thiazoyl; 5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl;  
 2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-  
 yl)-3-pyridazinyl; 6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl; 6-(4-



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- methoxypiperidinyl)-3-pyridyl; 6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridazinyl; 6-isopropoxy-3-pyridazinyl; 6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-pyridyl; 6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl; 6-(4-tetrahydropyranyloxy)-3-pyridazinyl; 6-morpholinylethoxy-3-pyridazinyl; 6-(4-ethoxypiperidinyl)-3-pyridazinyl; 6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl; 6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl; 6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl; 6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-pyridazinyl; 6-(3-(R)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(3-(S)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl; 6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl; 6-(1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(4-tertbutyl)piperidinyl)-3-pyridazinyl; 6-(4-N-formyl)piperidinyl)-3-pyridazinyl; 6-morpholinyl)-3-pyridazinyl; 4-N-1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide; 4-(4-dioxo-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl; 6-(3-methoxy-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(1,5-dioxo-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-yl)-3-pyridazinyl; 6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-pyridazinyl; 6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-((2S,3S)-2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridazinyl; 6-(4,4-(cis-1,2-dioxycyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1S,2S-dimethoxymethylethanedioxy)piperidinyl)-3-pyridazinyl; 6-(4,4-(cis-3,4-dioxy-oxacyclopentane)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-methoxypropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(1,3-dioxy-2-hydroxymethylpropylene)piperidinyl)-3-pyridazinyl; 6-(4,4-(2-(2,2-spiro-

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5 oxacyclopropane-1,3-dioxypropylene)piperidinyl)-3-pyridazinyl; 6-morpholinyl-3-  
pyridazinyl; 6-(4-morpholinyliminopiperidinyl)-3-pyridyl; 6-(4-(N-  
methylpiperazinyl)iminopiperidinyl)-3-pyridyl; 6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-  
10 3-pyridyl; 6-(4-ethylpiperidinylcarboxylate)-3-pyridyl; 2-phenylmethyl-3(2H)-  
5 pyridazinone-6-yl; 6-(4-(morpholinylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-  
morpholinylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N,N-  
15 dimethylaminocarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-methyl-N-  
methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-(N-  
methoxyethylcarboxamide)piperidinyl)-3-pyridyl; 6-(4-hydroxymethylpiperidinyl)-3-  
20 pyridyl; 6-(4-hydroxypiperidinyl)-3-pyridyl; 6-(4-N-acetyl-piperazinyl)-3-pyridyl; 6-(4-  
cyanopiperidinyl)-3-pyridyl; 6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl; 4-  
morpholinylbenzenesulfonamide; 4-N-4,4-ethylenedioxy-piperidinylbenzenesulfonamide;  
4-N-cyclopropylbenzenesulfonamide; 4-piperidinebenzenesulfonamide; 4-(4-  
25 cyanopiperidine)benzenesulfonamide; 4-N-cyclopropylmethylbenzenesulfonamide; 4-  
15 N,N-dimethylaminobenzenesulfonamide; 4-N-(S)-2-  
hydroxymethylpyrrolidinebenzenesulfonamide; 4-(4-  
hydroxypiperidine)benzenesulfonamide; 4-(cis-3,5-  
30 dimethylmorpholinyl)benzenesulfonamide; 3-fluoro-4-thiomorpholinylphenyl; 6-  
(thiomorpholinyl)-3-pyridyl; 6-(4,4-dioxothiomorpholinyl)-3-pyridyl; 4-(4,4-  
20 ethylenedioxy-piperidinylcarboxamide)phenyl; 4-(N-cyclopropylcarboxamide)phenyl; 4-  
(morpholinylcarboxamide)phenyl; 6-N-cyclopropylamino-3-pyridyl; 4-(4-  
35 hydroxypiperidinylcarboxamide)phenyl; 6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl;  
6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl; 6-hexahydropyrimidine-3-pyridyl; 6-(S)-2-  
ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl; 6-(cis-  
40 3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-[(3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-  
c]pyrrol-2-one-5-yl]-3-pyridyl; 6-(cis-2,3-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(S,R-2-  
hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl; 6-(R-2-hydroxymethyl-4-pyrrolidinyl)-  
45 3-pyridazinyl; 6-(1S,4S)-2-aza-5-oxa-bicyclo[2.2.1]heptane)-3-pyridyl; 6-(2-  
imidizolidone-1-yl)-3-pyridyl; 4-(2,4-(1H,3H)-quinazolin-3-yl)phenyl; 6-  
30 morpholinylcarboxamide-3-pyridazinyl; 6-methoxy-3-pyridazinyl; 6-N,N-

5 diethoxyethylamino-3-pyridazinyl; 6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl; 6-(4-(4-  
tetrahydropyranylmethyl)piperidinyl)-3-pyridazinyl; 6-(4-  
ethoxyethoxymethylpiperidinyl)-3-pyridazinyl; 6-N-methyl-N-1,3-  
10 dioxalanemethylamino-3-pyridazinyl; 6-(4,4-dioxyethylenecyclohexyloxy)-3-pyridazinyl;  
5 6-dihydroxymethylmethoxy-3-pyridazinyl; 6-(3-pyridyloxy)-3-pyridazinyl; 4,7-epoxy-7-  
methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl; 6-(4-N-methyl-N-methoxyethyl)-3-  
15 pyridazinyl; 6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-  
methylpyrrolidinyl)-3-pyridazinyl; 6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl; 6-  
(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl; 6-(cis-3-hydroxy-4-  
20 methylpyrrolidinyl)-3-pyridyl; 6-(trans-3-cyano-4-hydroxylpyrrolidinyl)-3-pyridyl; 6-(3-  
hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl; 6-(S-2-(4-  
tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl; 6-(2-(4-  
tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl; 2-morpholinyl-5-thiazoyl; 5-  
25 bromo-2-thienyl; 2,5-dimethyl-3-thienyl; 5-chloro-2-thienyl; 2,4-dimethyl-5-thiazoyl; 5-  
methyl-2-thienyl; 2-furanyl; 2-(4,4-dioxyethylenepiperidinyl)-5-thiazoyl; 3-thienyl; 3-  
methyl-2-thienyl; 2-morpholinyl-4-thiazoyl; 2-morpholinyl-4-trifluoromethyl-5-thiazoyl;  
15 5-morpholinyl-2-thienyl; 4-methyl-2-morpholinyl-5-thiazoyl; 2,5-dichloro-3-thienyl; 2,5-  
dimethyl-3-furanyl; N-methyl-2-pyrrolyl; 2-N,N-dimethylamino-5-thiazoyl; 2-  
morpholinyl-5-thiazoyl; 2-(4,4-dioxythiomorpholinyl)-5-thiazoyl; 1-N-methyl-2-  
20 morpholinyl-5-imidazolyl; 2-morpholinyl-5-oxazolyl; 2-N-methyl-N-methoxyethylamino-  
5-thiazoyl; 2-N-methyl-N-ethylamino-5-thiazoyl; 2-N-pyrrolidinyl-5-thiazoyl; 2-N-  
methyl-N-propylamino-5-thiazoyl; 2-N,N-diethylamino-5-thiazoyl; 2-(N-  
methypiperazinyl)-5-thiazoyl; 2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl; 2-N-methyl-N-(2-  
pyridylethyl)-5-thiazoyl; 2-(4-oxopiperazinyl)-5-thiazoyl; 2-(4-(N-  
40 morpholinyl)iminopiperazinyl)-5-thiazoyl; 6-N-morpholine-3-pyridinesulfonamide; 2-(4-  
oxopiperidinyl)-5-pyrimidyl; 2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl; 5-(4,4-  
dioxethylenepiperidinyl)-2-pyrazinyl; 5-(4-oxopiperidinyl)-2-pyrazinyl; 6-N-cyclopropyl-  
45 3-pyridinesulfonamide; 6-N-(4,4-dioxethylenepiperidinyl)-3-pyridinesulfonamide; 2-(4-  
(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl; 6-(4-  
30 (phenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(tert-butyloxy)iminopiperidinyl)-3-

pyridyl; 6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxyiminopiperidinyl)-3-pyridyl; 6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-methoxyethoxyiminopiperidinyl)-3-pyridyl; 6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-(4'-(5'H-2-oxyfuranyl)-4-hydroxy)piperidinyl)-3-pyridyl; 6-(4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl; 6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl; 6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl; 6-(3-hydroxyazetidyl)-3-pyridyl; 6-(cis-3-hydroxytropanyl)-3-pyridyl; 6-(cis-2,3-dihydroxypiperidinyl)-3-pyridyl; 6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyl; 6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl; 6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyl)-3-pyridazinyl; 6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl; 6-(trans-3,4-bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyl)-3-pyridyl; 6-(trans-3-hydroxytropanyl)-3-pyridyl; 6-(S,S-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridazinyl; 6-(R,R-trans-3,4-dihydroxypyrrolidinyl)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(8-(1-phenyl-1,3,8-triaza-2-spiro[4,5]deceN-4-one)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolyl)piperidinyl)-3-pyridazinyl; 6-(4-oxothiomorpholinyl)-3-pyridyl; 6-(4-(2-keto-1-benzimidazolyl)piperidinyl)-3-pyridyl; 6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl; 6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl; 6-N-(3-pyridylmethyl)amino-3-pyridyl; 6-(2-hydroxymethylpiperidinyl)-3-pyridyl; 6-(4-hydroxy-4-(4-

5 bromophenyl)piperidinyl)-3-pyridyl; 6-(4-N-(2-pyridinyl)piperazinyl)-3-pyridyl; 6-(4-N-(2-hydroxyethoxyethyl)piperazinyl)-3-pyridyl; 6-(4,4-diacetoxyethylthio)piperidinyl)-3-pyridyl; 6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl; 6-(4-pyrrolidinylpiperidinyl)-  
 10 3-pyridyl; 6-(4-N-cyanomethylpiperazinyl)-3-pyridyl; 6-(3-hydroxypyrrolidinyl)-3-pyridyl; 6-(4-methylpiperidinyl)-3-pyridyl; 6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl; 6-(4,4-difluoropiperidinyl)-3-pyridyl; 6-(4,4-dioxythiomorpholinyl)-3-pyridazinyl; 6-thiazolidinyl)-3-pyridyl; 6-(1,1-dioxythiazolidinyl)-3-pyridyl; 6-thiomorpholinyl)-3-pyridazinyl; 6-(2,5-dihydropyrrolyl)-3-pyridyl; 6-hydroxy-3-pyridazinyl; 6-piperidinyl)-3-pyridyl; and 6-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridyl; 6-morpholinyl)-3-pyridyl.  
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13. A compound according to claim 10 wherein R<sup>1</sup> is selected from the group consisting of:

25 (thiophene-2-yl)methyl; (thiophene-3-yl)methyl; butyl; cycloheptyl; pentyl; thiophene-2-yl; 1-(3-bromophenyl)ethyl; 2-(N-phenylmethoxycarbonyl)aminophenyl; 2-(3-bromophenyl)ethyl; 2-(3-cyanophenyl)methyl; 2-(4-bromophenyl)ethyl; 2-(5-chloro-2-(thiophen-3-yl)phenyl); 2-bromophenyl; 2-furanyl; 2-methylpropyl; 2-phenylethyl; phenylmethyl; 2,3-dimethoxyphenyl; 2,3-methylenedioxyphenyl; 3-(furan-2-yl)phenyl; 3-(thiophen-2-yl)phenyl; 3-(2-pyridyl)phenyl; 3-(3-methoxybenzyl)phenyl; 2-(3-aminopropynyl)phenylmethyl; 3-benzyloxyphenyl; 3-bromo-4-fluorophenyl; 3-bromo-5-iodophenyl; 3-bromo-5-methoxyphenyl; 3-bromophenyl; 3-bromophenyl)methyl; 3-carboxamidophenyl; 3-chlorophenyl; 3-cyanophenyl; 3-diethylmalonylallylphenyl; 3-dimethylaminophenyl; 3-ethoxyphenyl; 3-fluoro-5-trifluoromethylphenyl; 3-fluorophenyl; 3-hydroxyphenyl; 3-iodophenyl; 3-methoxyethoxyphenyl; 3-methoxyphenyl; 3-methylphenyl; 3-methylsulfonylphenyl; 3-methylthiophenyl; 3-t-butylacrylphenyl; 3-trifluoromethoxyphenyl; 3-trifluoromethylphenyl; 3-vinylpyridinylphenyl; 3,4-dichlorophenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; 3,5-di(trifluoromethyl)phenyl; 3,5-dibromophenyl; 3,5-dichlorophenyl; 3,5-dimethoxyphenyl; 3,5-dimethylphenyl; 4-(2-propyl)phenyl; 4-(2-propyl)oxyphenyl; 4-benzyloxyphenyl; 4-bromophenyl; 4-bromothiophene-2-yl; 4-butoxyphenyl; 4-

dimethylaminophenyl; 4-fluoro-3-trifluoromethylphenyl; 4-methoxyphenyl; 4-neopentylphenyl; 4-phenoxyphenyl; 5-bromothiophene-2-yl; 5-cyclohexyl; 5-cyclopropyl; 5-hexyl; 5-methyl; 5-phenyl; (2-bromo-5-chlorophenyl)methyl; (2-bromophenyl)methyl; (5-chloro-2-(3-methoxyphenyl)phenyl)methyl; 3-bromophenyl; 2-pyridyl; 2-ethoxyphenyl; 5-ethoxyphenyl; 2,5-dichlorophenyl; 2,5-dimethylphenyl; 3-fluorophenyl; 3-trifluoromethylphenyl; 5-trifluoromethylphenyl; 3,5-dichlorophenyl; 4-bromo-2-thienyl; 3-bromo-2-thienyl; 3-cyanophenyl; 4-tetrahydropyranyl; 3-indolyl; 5-indolyl; 4-quinolyl; 2-bromophenyl; 4-fluorophenyl; 4,4-difluorocyclohexyl; 1,1-dimethyl-3-butenyl; 2,3-dichlorophenyl; isopropyl; and 2-trifluorophenylphenyl.

14. A compound according to claim 10 selected from the group consisting of:
- 4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl)-3-pyridinylpyrido[2,3-d]pyrimidine;
- 4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl)-3-pyridinylpyrido[2,3-d]pyrimidine;
- 4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl)-3-pyridinylpyrido[2,3-d]pyrimidine;
- 4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl)-3-pyridinylpyrido[2,3-d]pyrimidine;
- (S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- (S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy)piperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(4-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

15

d]pyrimidine;

4-amino-5-(4-dimethylaminophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(4-(2-propyl)phenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-neopentylphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(4-butyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(4-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-(2-propyl)oxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-butoxyphenyl)-7-(4-N-formylpiperazinylphenyl)pyrido[2,3-

d]pyrimidine;

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25

4-amino-5-(4-benzyloxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-phenoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-(2-propyl)phenyl)-7-(4-diethylmalonylallylphenyl)pyrido[2,3-

45

d]pyrimidine;

4-amino-5-(4-(2-propyl)phenyl)-7-(4-t-butylacetylphenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,4-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-t-butylacrylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-diethylmalonylallylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-vinylpyridinylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-carboxamidophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-cyanophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-benzyloxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-butoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-(2-pyridyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-methylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-methoxyphenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-phenylpyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-ethylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-cyanophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-hydroxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-iodophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-ethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-trifluoromethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3,5-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-hydroxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-(imidazol-1-yl)phenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-isopropylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-trifluorophenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-(3-methoxybenzyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-methoxyethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,4-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

40

25 d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-ethoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2'-thiophene)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(4-fluorophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-dimethylaminophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

30 d]pyrimidine;

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4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,4,5-trimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-nitrophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3,4-methylenedioxyphenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(thiophen-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(thiophen-2-yl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3-bromophenyl)-7-(4-carboxamidophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(4-(2-methoxyethoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

25

15 4-amino-5-(3-trifluoromethylphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-aminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromo-4-fluorophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3,5-dimethoxyphenyl)-7-(4-imidazolylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(thiophene-2-yl)phenyl)pyrido[2,3-

35

d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(4-(3-pyridyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(4-methylpiperidiny)phenyl)pyrido[2,3-

40

25 d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-

30 d]pyrimidine;

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4-morpholinyl-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(5-bromothiophene-2-yl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(acetylamino)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethoxyphenyl)-7-(5-pyrimidinylphenyl)pyrido[2,3-d]pyrimidine;

20

10 4-(4-fluorophenyl)amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-bromothiophene-2-yl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(5-(dimethylamino)thiophene-2-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-iodophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-di(trifluoromethyl)phenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3,5-dibromophenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-(4-methylpiperidinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3,5-dibromophenyl)-7-(4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(3-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-methoxyphenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-(methylthio)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3,4-dichlorophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(3-bromophenyl)-7-(3-amino-4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-trifluoroacetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(dimethylamino)-3-fluorophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-ethyl-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

35

4,4-bis(acetyl amino)-5-(3-bromophenyl)-7-(4-(N-methyl-N-acetyl amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-ethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-ethyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-(3-methoxypropionyl)-N-isopropylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-(2-(dimethylamino)ethyl)-N-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-(2-(dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-cyano)ethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(3-methoxy)propionylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-formyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(4-methoxy-2-butyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-(N-phthalimidyl)acetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-methyl-N-(trifluoroacetyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-methyl-4-(N-acetyl-N-methylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-cyanophenyl)-7-(4-methylsulfonylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-cyanophenyl)-7-(4-(N-methyl-N-formylamino)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-formylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methoxyethylamino)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(dimethylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(2-(N-methoxyethyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(N-formyl-N-methyl amino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(2-(N-methylamino)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(2-(1-pyrrolidinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(1-morpholinyl)-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(2-oxo-3-oxazolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-(thiophen-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-(furan-2-yl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-(3-methoxyphenyl)phenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-phenyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-chlorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-(morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-chlorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-chlorophenyl)-7-(4-(thiophen-2-yl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(4-(5-pyrimidinyl)phenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromo-4-fluorophenyl)-7-(4-iodophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromothiophene-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)methyl-7-(4-(dimethylamino)phenyl)pyrido[2,3-

10 d]pyrimidine;

20

4-amino-5-(2-phenylethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-methylpropyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(butyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(2-(4-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-

15 d]pyrimidine;

4-amino-5-(butyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-cyanophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

30

d]pyrimidine;

4-amino-5-(2-(N-phenylmethoxycarbonyl)aminoethyl)-7-(4-

20 dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(cycloheptyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-(5-chloro-2-(thiophen-3-yl)phenyl)methyl)-7-(4-

dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(pentyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-hexyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-

d]pyrimidine;

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4-amino-5-((2-bromophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-

d]pyrimidine;

30 4-amino-5-cyclopropyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-((2-bromo-5-chlorophenyl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-methyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(2,3-methylenedioxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

10 4-amino-5-(3,5-dimethylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3,4-dichlorophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(4-fluoro-3-trifluoromethylphenyl)-7-(4-

15 dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-morpholinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-piperidinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromo-5-methoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-methylthiophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

25 d]pyrimidine;

4-amino-5-(3-bromo-5-methoxyphenyl)-7-(thiophene-2-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2,3-dimethoxyphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(3-methylsulfonylphenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-

30 d]pyrimidine;

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- 5 4-acetyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 10 4-formyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 5 4-(methoxyacetyl)-amino-5-(3-bromophenyl)-7-(4-diethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 15 4-trifluoroacetyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 10 4-pentanoyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 20 4-benzoyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 25 4-(N-BOC-glycyl)-amino-5-(3-bromophenyl)-7-(4-  
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 15 4-(N-phthalimidylglycyl)-amino-5-(3-bromophenyl)-7-(4-  
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 30 4-(ethoxycarbonyl)-amino-5-(3-bromophenyl)-7-(4-  
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 20 4-(ethylaminocarbonyl)-amino-5-(3-bromophenyl)-7-(4-  
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 35 4-allyl-amino-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-  
d]pyrimidine;
- 40 4-(2-(N,N-dimethylamino)ethyl-amino)-5-(4-bromophenyl)-7-(4-  
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 25 4-(4-(N,N-dimethylamino)butyl-amino)-5-(3-bromophenyl)-7-(4-  
dimethylaminophenyl)pyrido[2,3-d]pyrimidine;
- 45 4-(N-allyl-N-formyl-amino)-5-(4-dimethylaminophenyl)-7-(4-  
bromophenyl)pyrido[2,3-d]pyrimidine;
- 30 4-diacetyl-amino-5-(p-dimethylaminophenyl)-7-(4-  
bromophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-amino-2-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-

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pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-dimethylamino-2-

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pyrazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(1-methyl-2-oxobenzoxazolin-6-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-((5-chloro-2-(3-methoxyphenyl)phenyl)methyl)-7-(4-

10 

dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-((thiophene-2-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-((thiophene-3-yl)methyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((2-bromophenyl)methyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-formyl-N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-(2-methoxyethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-((2-dimethylamino)ethyl)amino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(2-methoxy)acetylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-((4-formylamino)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)acetylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(2-oxo-3-oxazolidinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(2-propyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-4-pyrrolidinylphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-phenylmethyl-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-(3-aminopropynyl)phenylmethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(1-(3-bromophenyl)ethyl)-7-(4-diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-dimethylaminophenyl)-7-(4-bromophenyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(2-furanyl)-7-(4-(N-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(2-dimethylamino-5-pyrimidinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(ureido)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-phenylmethyl-3-piperidinyl)-7-(4-

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diethylaminophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-methyl-5-isoxazolyl))-3-

pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-chloro-3-pyridinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridinyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1,2,4-triazol-4-yl)-3-pyridinyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-pyrimidinyl)pyrido[2,3-

d]pyrimidine;

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4-amino-5-(2-thiazolyl)-7-(4-pyrrolidinylphenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-pyrazolyl-3-pyridinyl)-pyrido[2,3-

d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-ureido)phenyl)-pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-(2-pyrimidinyl)amino)phenyl)-  
pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-methylamino)phenyl)-  
pyrido[2,3-d]pyrimidine;

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4-formylamino-5-(3-bromophenyl)-7-(3-fluoro-4-(N-formyl-N-  
methylamino)phenyl)-pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(4-(N-methyl-N-methylsulfonylamino)-  
phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-methylsulfonylamino)-3-  
pyridinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(1-methyl-5-benzimidazolyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-pyrrolidinyl-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-pyrazinyl)pyrido[2,3-  
d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(5-(N-(2-methoxyethyl)-N-methylamino)-2-  
pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(morpholinylmethyl)-phenyl)pyrido[2,3-  
d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(5-(N,N-bis(2-methoxyethyl)amino)-2-  
pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(imidazolylmethyl)-phenyl)pyrido[2,3-  
d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(1-morpholinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(4-((dimethylamino)methyl)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(4-hydroxy-1-piperidinyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(5-(N-formyl-N-methylamino)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(5-(2-propenyl)-2-pyridinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(3-(2-methoxyethyl)-2-oxo-6-benzoxazolyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-(1-(N-formylamino)-ethyl)phenyl)pyrido[2,3-d]pyrimidine;

15

4-(methylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

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4-(2-methoxyethylamino)-5-(3-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine hydrochloride;

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-2-imidazolyl)phenyl)pyrido[2,3-d]pyrimidine trihydrochloride;

35

4-amino-5-(3-bromophenyl)-7-(4-(aminomethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-bromo-4-(dimethylamino)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(dimethylaminoethyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(3-(dimethylamino)propynyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(3-amino-3-methylbutynyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-dimethylphosphonatophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(3-(methoxypropynyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-carboxyphenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(2-(dimethylamino)ethyl)-3-oxo-2H-4H-pyrido[3,2-b]-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,3-dihydro-3-(dimethylaminoethyl)-2-

10 oxobenzoxazol-6-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-methyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,2,4-trimethyl-3-oxo-2H-4H-benzo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(4-(2-dimethylamino)ethyl)-2H-4H-benzo-3-oxo-1,4-oxazin-7-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-(1-methylethyl)-2-pyridyl)pyrido[2,3-

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d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-piperidin-1-ylpyrid-2-yl)pyrido[2,3-

20 d]pyrimidine;

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4-amino-5-(1-(4-bromophenyl)ethyl)-7-(6-morpholinylpyrid-3-yl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-((N-formylamino)methyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(1-methyl-1-(N-methylamino)ethyl)phenyl)-pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-(1-(dimethylamino)-1-

45

methylethyl)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(N-acetyl-5-indolyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-diethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(4-(N-methyl-N-formyl)amino)-phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-ethylpropyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclopentyl-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(2-chloro-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dimethylcyclohexyl)-7-(6-dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-((N-(benzyloxycarbonyl)-4-piperidinyl)methyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-bromo-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(3-cyanophenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-dimethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-imidazolyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(azacycloheptanyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(1-methylethyl)amino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-acetyl piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-acetyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-methyl-1,4-diazacycloheptanyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(2-(2-pyridyl)ethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(2-(N,N'-dimethylaminoethyl)-N-methylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-azetidiny-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(3-(N-methylacetamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(3-(formamido)pyrrolidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(2-methoxymethyl)pyrrolidin-1-yl)pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(N-methoxyethyl-N-propylamino)pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(N-methyl-N-(2,2-dimethoxyethyl)amino)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-(dimethylamino)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-(aminocarbonyl)piperidinyl)pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(N-methyl-N-(3-(diethylamino)propyl)aminopyrid-3-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(4-pyridyl)ethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(N-methyl-N-(3-pyridylmethylamino)pyrid-3-yl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-5-indolyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1-(2-bromophenyl)ethyl)-7-(1-methyl-2,3-dioxo-5-indolyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-(1-morpholinyl)phenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-hydroxy-3-nitrophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-formylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromo-4-methoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-chlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-chloro-6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-oxido-morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-N-formylamino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-(2-hydroxyethoxyethyl)-3-pyridyl-N-oxide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy)morpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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1-(5-(4-amino-5-(3-bromophenyl)pyrido[2,3-d]pyrimidin-7-yl)-2-pyridyl)-piperidine-4-phosphate, disodium salt;

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4-amino-5-(3-bromophenyl)-7-(4-methylenylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-hydroxy-4-(hydroxymethyl)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-cyclohexyl-7-(6-(4-oxo-piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-cyclohexyl-7-(6-(4-methylenylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-N-(iminomethyl)amino-5-cyclohexyl-7-(6-(dimethylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-allylamino-5-(4-bromophenyl)-7-(4-dimethylaminophenyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(cyclohexyl)-7-(6-(4,4-ethylenedioxy piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazolyl)pyrido[2,3-d]pyrimidine;

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4-(N-(2,3-dihydroxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-(N-(3-morpholinylpropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-(N-(2-(4-imidazolyl)ethyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-(N-(3-carboxypropyl)amino)-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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(S)-4-amino-5-(3-bromophenyl)-7-(6-(O-methyl-2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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(S)-4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethylpyrrolidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-fluorophenyl)-7-(6-(4,4-ethylenedioxy piperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4,4-ethylenedioxy piperidinyl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazolyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(N-methyl-3-indolyl)-7-(6-morpholinyl-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxycarbonylmethoxyiminopiperidinyl)-3-pyridinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-oxopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridazyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxyiminopiperidinyl)-3-

20

pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-phenylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-methoxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-isobutoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-tetrahydropyranyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-morpholinylethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrapyranyloxyethyl)piperidinyl)-3-

45

pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-(R)-tetrahydrofuranlyloxy)piperidinyl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3-(S)-tetrahydrofuranyloxy)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-bis-ethoxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-ethoxy-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-amino-4-hydroxy)pyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-pyridyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2,3-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-pyridyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2-ethoxyphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromo-5-ethoxyphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(2,5-dichlorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2,5-dimethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine

4-amino-5-(3-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-trifluoromethylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-

5  
d]pyrimidine;

4-amino-5-(3-fluoro-5-trifluoromethylphenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-

15

3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3,5-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-

pyridyl)pyrido[2,3-d]pyrimidine;

10  
4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-

20

pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-bromo-2-thienyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-

pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-tertbutyl)piperidinyl-3-pyridazinyl)pyrido[2,3-

15  
d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-formyl)piperidinyl-3-pyridazinyl)pyrido[2,3-

d]pyrimidine;

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4-amino-5-(3-bromo-2-thienyl)-7-(6-(4,4-ethylenedioxypiperidinyl)-3-pyridyl)pyrido[2,3-

d]pyrimidine;

20  
4-amino-5-(3-cyanophenyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-Bromophenyl)-7-(6-(S-O-ethyl-2-hydroxymethylpyrrolidinyl)-3-

pyridazinyl)pyrido[2,3,

d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-((2S,3S)-2,3-dimethyl-1,4-dioxo-8-azaspiro[4.5]decan-

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8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-1,2-dioxycyclopentyl)piperidinyl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-1-oxa-4,8-diazaspiro[4.5]decan-8-yl)-3-

pyridazinyl)pyrido[2,3-d]pyrimidine;

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- 5 4-amino-5-(3-bromophenyl)-7-(6-((2R,3R)-2,3-bis(methoxymethyl)-1,4-dioxo-8-  
azaspiro[4.5]decan-8-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(4,4-(cis-3,4-dioxy-oxacyclopentyl)piperidinyl)-3-  
pyridazinyl)pyrido[2,3-d]pyrimidine;
- 5 4-amino-5-(3-bromophenyl)-7-(6-(3-methoxy-1,5-dioxo-9-azaspiro[5.5]undecan-9-yl)-3-  
pyridazinyl)pyrido[2,3-d]pyrimidine;
- 15 4-amino-5-(3-bromophenyl)-7-(6-(1,5-dioxo-3-hydroxymethyl-9-azaspiro[5.5]undecan-9-  
yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 10 4-amino-5-(3-bromophenyl)-7-(6-(1,7,14-trioxa-11-azadispiro[4.2.5.2]pentadecan-11-yl)-  
3-pyridazinyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(4-tetrahydropyranyl)-7-(6-morpholinyl-3-pyridazinyl)pyrido[2,3-  
d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(6-(4-morpholinyliminopiperidinyl)-3-pyridyl)pyrido[2,3-  
d]pyrimidine;
- 25 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methylpiperazinyl)iminopiperidinyl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-(1,2,4-triazol-1-yl)iminopiperidinyl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine;
- 4-amino-5-(3-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 20 4-amino-5-(5-indolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;
- 35 4-amino-5-(3-bromophenyl)-7-(6-(4-ethylpiperidinylcarboxylate)-3-pyridyl)pyrido[2,3-  
d]pyrimidine;
- 4-amino-5-(3-bromophenyl)-7-(2-phenylmethyl-3(2H)-pyridazinone-6-yl)pyrido[2,3-  
d]pyrimidine;
- 40 4-amino-5-(3-bromophenyl)-7-(6-(4-(morpholinylcarboxamide)piperidinyl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine;
- 45 4-amino-5-(3-bromophenyl)-7-(6-(4-(N-morpholinylaminocarboxamide)piperidinyl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine;
- 30 4-amino-5-(3-bromophenyl)-7-(6-(4-(N,N-dimethylaminocarboxamide)piperidinyl)-3-  
pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methyl-N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-quinolyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-methoxyethylcarboxamide)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxymethylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(2-bromophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(2-bromophenyl)-7-(6-(4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-N-acetyl piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-cyanopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-(4-fluorophenyl)piperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(4-fluorophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-morpholinylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-1,4-dioxo-8-azaspiro[4.5]decan-8-ylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-piperidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(4-cyanopiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-N-cyclopropylmethylbenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N,N-dimethylaminobenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-N-(S)-2-

hydroxymethylpyrrolidinebenzenesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidine)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(4-(cis-3,5-

dimethylmorpholinyl)benzenesulfonamide)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(3-fluoro-4-thiomorpholinylphenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(4-fluorophenyl)-7-(6-(thiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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10 4-amino-5-(4-fluorophenyl)-7-(6-(4,4-dioxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-methoxy-5-(3-bromophenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(4-(4-dioxo-8-azaspiro[4.5]decan-8-ylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(4-(N-cyclopropylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(4-(morpholinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropylamino-3-pyridyl)pyrido[2,3-d]pyrimidine;

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20 4-amino-5-(3-bromophenyl)-7-(4-(4-hydroxypiperidinylcarboxamide)phenyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(S)-hydroxymethylpyrrolidinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-ethoxyethoxy)piperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-hexahydropyrimidine)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(4,4-difluorocyclohexyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(S)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(R)-2-ethoxyethoxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3,4-dihydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-((3aR,6aS)-2-oxo-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypyrrolidinyl)-3-

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pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(S,R-2-hydroxymethyl-4-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(R-2-hydroxymethyl-4-pyrrolidinyl)-3-

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pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(2-imidizolidone-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(1,1-dimethyl-3-butenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)-3-

35

pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-carboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-morpholinylcarboxamide-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-methoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N,N-diethoxyethylamino-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxymethyl)piperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-ethoxyethoxymethylpiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-N-methyl-N-1,3-dioxalanemethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(1,4-dioxaspiro[4.5]decanyl-8-oxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-dihydroxymethylmethoxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3-pyridyloxy)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4,7-epoxy-7-methyl-2,3,3A,4,5,6,7,7a-octahydro-1H-isoindolyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-ethyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-N-methyl-N-methoxyethyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3,4-dimethoxymethoxypyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(hexahydro-1H-furo[3,4-c]pyrrol-5-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-

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pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-3-hydroxy-4-methylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3-cyano-4-hydroxylpyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxy-4-tert-butylcarboxamidopyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(S-2-(4-tetrahydropyranyloxy)methylpyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyranyloxy)iminopyrrolidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-bromo-2-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-thienyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-chloro-2-thienyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(2,4-dimethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(5-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-furanyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(2-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(3-thienyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(3-methyl-2-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-4-trifluoromethyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(5-morpholinyl-2-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(4-methyl-2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2,5-dichloro-3-thienyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2,5-dimethyl-3-furanyl)pyrido[2,3-d]pyrimidine;

30 4-amino-5-(3-bromophenyl)-7-(N-methyl-2-pyrrolyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-N,N-dimethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxythiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(1,1-dioxidothiomorpholinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-morpholinyl-5-oxazolyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-methoxyethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-ethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N-pyrrolidinyl-5-thiazoyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-propylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-N,N-diethylamino-5-thiazoyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(2-(N-methylpiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(N-(2-pyridyl)piperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-N-methyl-N-(2-pyridylethyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4-(N-morpholinyl)iminopiperazinyl)-5-thiazoyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-N-morpholine-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4-oxopiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4,4-dioxethylenepiperidinyl)-5-pyrimidyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(5-(4-oxopiperidinyl)-2-pyrazinyl)pyrido[2,3-d]pyrimidine;  
4-amino-5-(3-bromophenyl)-7-(6-N-cyclopropyl-3-pyridinesulfonamide)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(N-1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridylsulfonamide)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(2-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-5-pyrazinyl)pyrido[2,3-d]pyrimidine;  
4-amino-5-(3-bromophenyl)-7-(6-(4-(phenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(tert-butyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(cyclohexyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(2-thenylmethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-hydroxy-2-furanyl)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(4'-acetyl-4'-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(isopropylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methylcarboxymethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(2-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(allyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(ethoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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15 4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(methoxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(1-(hydroxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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20 4-amino-5-(3-bromophenyl)-7-(6-(4-(2-tetrahydropyranyloxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(isopropylcarboxymethoxy)iminopiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(1-(4-tetrahydropyranyloxy)iminoethyl))-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25 4-amino-5-(3-bromophenyl)-7-(6-(4-(3-butyrolactone)-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

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30 4-amino-5-(3-bromophenyl)-7-(6-(4-acetyl-4-hydroxypiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxyazetidiny)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-((1R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(cis-2,3-dihydroxypiperidiny)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(3-pyridylmethyl)amino)-3-pyridazinyll)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1,2,3,6-tetrahydropyridyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(4-(N-4'-methoxyphenylcarbamoyl)piperidinyll)-3-pyridazinyll)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-butyrolactone)-4-hydroxypiperidinyll)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(trans-3,4-bis(N-4'-methoxyphenylcarbamoyl)pyrrolidinyll)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-((1S,5R)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(S,S-trans-3,4-dihydroxypyrrolidinyll)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyll)-3-pyridazinyll)pyrido[2,3-d]pyrimidine;

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4-amino-5-(3-bromophenyl)-7-(6-(R,R-trans-3,4-dihydroxypyrrolidinyll)-3-pyridyl)pyrido[2,3-d]pyrimidine;

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25

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-oxo-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4,4-dioxido-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

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5

4-amino-5-(3-bromophenyl)-7-(6-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)l)piperidiny)l)-3-pyridaziny)l)pyrido[2,3-d]pyrimidine;

5 4-amino-5-(3-bromophenyl)-7-(6-(4-oxothiomorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-(2-keto-1-benzimidazoliny)l)piperidiny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(2-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(N-methyl-N-(4-pyridylethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

25

4-amino-5-(3-bromophenyl)-7-(6-N-(3-pyridylmethyl)amino-3-pyridyl)pyrido[2,3-d]pyrimidine;

15 4-amino-5-(3-bromophenyl)-7-(6-(2-hydroxymethyl)piperidiny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-(1-oxa-4-thia-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(4-hydroxy-4-(4-bromophenyl)piperidiny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20 4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-pyridnyl)piperaziny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

40

4-amino-5-(3-bromophenyl)-7-(6-(4-N-(2-hydroxyethoxyethyl)piperaziny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

25 4-amino-5-(3-bromophenyl)-7-(6-(4,4-diacetoxyethylthio)piperidiny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(N-methy-N-(3-pyridylmethyl)amino)-3-pyridyl)pyrido[2,3-d]pyrimidine;

50

30 4-amino-5-(3-bromophenyl)-7-(6-(4-pyrrolidiny)l)piperidiny)l)-3-pyridyl)pyrido[2,3-d]pyrimidine;

55

5

4-amino-5-(3-bromophenyl)-7-(6-(2-(1H-imidazol-4-yl)ethylamino)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

10

4-amino-5-(3-bromophenyl)-7-(6-(4-N-cyanomethylpiperazinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

5

4-amino-5-(3-bromophenyl)-7-(6-(3-hydroxypyrrolidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

15

4-amino-5-(3-bromophenyl)-7-(6-(4-methylpiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(cis-3,5-dimethylmorpholinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(4,4-difluoropiperidinyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiomorpholinyl)-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

25

15

4-amino-5-(3-bromophenyl)-7-(6-thiazolidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-(1,1-dioxidothiazolidin-3-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

30

4-amino-5-(3-bromophenyl)-7-(6-thiomorpholinyl-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

20

4-amino-5-(3-bromophenyl)-7-(6-(2,5-dihydropyrrolyl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

35

4-amino-5-(3-bromophenyl)-7-(6-(1,3-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-(3-bromophenyl)-7-(6-hydroxy-3-pyridazinyl)pyrido[2,3-d]pyrimidine;

40

25

amino-5-(2,3-dichlorophenyl)-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

4-amino-5-isopropyl-7-(6-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine;

45

4-amino-5-(3-bromophenyl)-7-(6-piperidinyl-3-pyridyl)pyrido[2,3-d]pyrimidine;

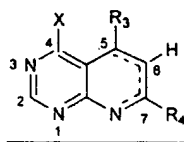
50

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4-amino-5-(3-bromophenyl)-7-(6-(3-(4-tetrahydropyran-2-yl)oxyimino)pyrrolidin-1-yl)-3-pyridyl)pyrido[2,3-d]pyrimidine; and  
 4-amino-5-(2-trifluorophenylphenyl)-7-(6-morpholinyl-3-pyridyl)pyrido[2,3-d]pyrimidine.

15. A pharmaceutical composition comprising a compound according to Claim 10 and a pharmaceutically acceptable carrier.

16. A compound of formula III



III,

wherein X is selected from the group consisting of hydroxy and halogen;

$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl,  $(NZ_1Z_2)$ alkyl, and  $-R^A R^B$ ;

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxy, carbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxy, and formyl;

$R^A$  is selected from the group consisting of aryl and arylalkyl;

$R^B$  is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

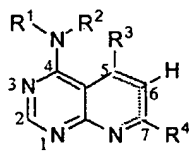
$R^C$  is selected from the group consisting of aryl, arylalkyl, heterocycle, and heterocyclealkyl;

$R^D$  is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

5  $R^E$  is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and a dashed line --- indicates that a double bond is optionally  
 10 present provided that proper valencies are maintained.

15 17. A compound according to claim 15 wherein said compound is an intermediate in a process to produce a compound according to claim 10.

20 18. A process for the preparation of an adenosine kinase inhibiting compound of formula I



I,

wherein:

15  $R^1$  and  $R^2$  are hydrogen;

$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ<sub>1</sub>Z<sub>2</sub>)alkyl, and -R<sup>A</sup>R<sup>B</sup>;

20  $Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

$R^A$  is selected from the group consisting aryl and arylalkyl;

40  $R^B$  is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

45 25  $R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and -R<sup>C</sup>R<sup>D</sup>R<sup>E</sup>;

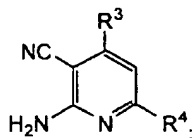
$R^C$  is selected from aryl, arylalkyl, heterocycle, and heterocyclealkyl;

$R^D$  is selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

$R^E$  is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;  
the method comprising:

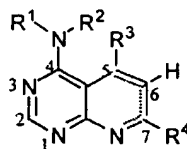
- (a) reacting a ketone having the formula  $R^4$ -CO-CH<sub>3</sub>, wherein  $R^4$  is as defined above, with an aldehyde having the formula  $R^3$ -CHO, wherein  $R^3$  is as defined above and malononitrile in the presence of an ammonium salt under anhydrous conditions and
- isolating a first intermediate compound having the structure



- (b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5,6 carbons and a double bond between the 7 carbon and the 8 nitrogen and then,

- (c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

19. A process for the preparation of an adenosine kinase inhibiting compound having the formula



(I),

wherein:

$R^1$  and  $R^2$  are hydrogen;

$R^3$  is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ, $Z_2$ )alkyl, and  $-R^A R^B$ ;

$Z_1$  and  $Z_2$  are each independently selected from the group consisting of hydrogen, alkoxy, alkyl, alkylcarbonyl, benzyl, benzyloxy, and formyl;

$R^A$  is selected from the group consisting of aryl and arylalkyl;

$R^B$  is selected from aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl;

$R^4$  is selected from the group consisting of alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, and  $-R^C R^D R^E$ ;

$R^C$  is selected from aryl, arylalkyl, heterocycle, and heterocyclealkyl;

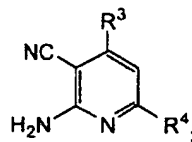
$R^D$  is selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

$R^E$  is absent or selected from aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

a dashed line --- indicates that a double bond is optionally present provided that proper valencies are maintained;

the method comprising

(a) reacting a ketone having the formula  $R^4C(O)CH_3$ , wherein  $R^4$  is as defined above, with an dicyanoalkene compound having the formula  $R^3CH=C(CN)_2$ , wherein  $R^3$  is as defined above by heating at reflux and isolating a first intermediate compound having the structure



(b) reacting the first intermediate compound with formamide at reflux for from about 1 to about 8 hours, and isolating the compound of formula I which has a double bond between the 5 and 6 carbons and a double bond between the 7 carbon and the 8 nitrogen and

(c) optionally reducing the compound from step (b) to form a partially reduced or fully reduced right side of formula I by catalytic hydrogenation.

# INTERNATIONAL SEARCH REPORT

|   |   |  |
|---|---|--|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 C07D471/04 A61K31/519 A61P25/00 A61P9/00 C07D519/00<br>//(C07D471/04, 239:00, 221:00), (C07D519/00, 471:00, 451:00),<br>(C07D519/00, 471:00, 471:00)  |   | International Application No.<br>PCT/US 99/24901                 |
| According to International Patent Classification (IPC) or to both national classification and IPC   |   |  |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 C07D A61K A61P  |   |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched   |   |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  |   |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>   |   |  |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
| X   | SWATI ET AL: "SYNTHESIS AND ANTIMICROBIAL<br>EVALUATION OF SOME SUBSTITUTED PYRIDO<br>U2,3-DIPYRIMIDINES"<br>INDIAN JOURNAL OF PHARMACEUTICAL<br>SCIENCES, XX, XX,<br>vol. 57, no. 6,<br>1 November 1995 (1995-11-01), pages<br>229-232, XP002071942<br>Bombay, India<br>ISSN: 0250-474X<br>table, compounds IIIa-IIIc<br>---<br>-/-- | 7, 10, 11,<br>15   |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.   |   |  |
| * Special categories of cited documents :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier document but published on or after the international filing date<br>"L" document which may throw doubts on priority claims) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>"Δ" document member of the same patent family |   |  |
| Date of the actual completion of the international search<br>9 March 2000   |   | Date of mailing of the international search report<br>22/03/2000 |
| Name and mailing address of the ISA<br>European Patent Office, P B 5818 Patentlaan 2<br>NL - 2220 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016   |   | Authorized officer<br>Alfaro Faus, I                             |

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Int. onal Application No  
PCT/US 99/24901

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
|--|---|-----------------------|
| Category *   | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| X  | SWATI ET AL: "SYNTHESIS OF SOME PYRIDOU2,3-DPYRIMIDINE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY" HETEROCYCLIC COMMUNICATIONS,IL,FREUND PUBLISHING HOUSE, TEL AVIV, vol. 1, no. 1, 1 January 1994 (1994-01-01), pages 89-94, XP002071943<br>ISSN: 0793-0283<br>tables 1 and 2, compounds 6a, 6b<br>---                         | 7,10,11,<br>15        |
| X  | PRAKASH L ET AL: "SYNTHESIS OF SOME NEW 5, 7-DISUBSTITUTED PYRIDO (2,3-D) PYRIMIDINE DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITY" INDIAN JOURNAL OF HETEROCYCLIC CHEMISTRY,IN,R.S. VERMA, LUCKNOW, vol. 1, no. 1, 1 June 1991 (1991-06-01), pages 21-25, XP002071944<br>ISSN: 0971-1627<br>table 1, compounds IIa and IIb<br>--- | 7,10,11,<br>15        |
| X  | A. GUPTA-SHAHILA ET AL.: "Condensation products of 2-amino-3-cyano-4,6-disubstituted pyridine with carbon disulfide, thiourea, urea & formamide and their bacterial activity" IL FAMACO, vol. 47, no. 6, 1992, pages 979-983, XP002132601<br>Pavia, Italy<br>table I, compounds IIA and IIB<br>---                                | 7,10,11,<br>15        |
| X  | DAVE C G ET AL: "PYRIDOPYRIMIDES: PART III-SYNTHESIS AND ANALGESIC ACTIVITY OF 4-AMINOPYRIDO U2,3-DPYRIMIDINES" INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES,XX,XX, vol. 48, no. 3, 1 May 1986 (1986-05-01), pages 75-77, XP002071945<br>ISSN: 0250-474X<br>table I, compounds IIB-IIe<br>---  | 7,10-12,<br>15        |
| X  | DAVE C G ET AL: "DIETHYL ETHOXYMETHYLENEMALONATE IN TRIHETEROCYLCES: A NEW SYNTHESIS OF PYRIDOU3,2-EPYRIMIDOU1,2-CPYRIMIDINES" JOURNAL OF HETEROCYCLIC CHEMISTRY., 1 November 1997 (1997-11-01), XP002071947<br>HETEROCORPORATION. PROVO., US<br>ISSN: 0022-152X<br>page 1806, compounds 2a-2d<br>---                             | 10-12                 |
|  | -/--  |                       |

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/24901

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | BAYOUMY B E ET AL: "NEW SYNTHESIS OF PYRIDOPYRIMIDINE AND PYRIOTETRAHYDROQUINOLINE DERIVATIVES" CHEMICAL ABSTRACTS, US, AMERICAN CHEMICAL SOCIETY, COLUMBUS, vol. 116, no. 9, 2 March 1992 (1992-03-02), page 816 XP002071948<br>ISSN: 0009-2258<br>-& DATABASE CHEMICAL ABSTRACTS 'Online! Chemical Abstracts Service, Columbus XP002132602<br>compounds with RNs '138744-54-4! '138744-55-5! '138744-56-6! '138744-57-7!<br>& ZHONGHUA YAOXUE ZAZHI, vol. 43, no. 5, 1991, pages 365-71,<br>---- | 10,11,16              |
| X          | ROBINS R K ET AL: "STUDIES ON CONDENSED PYRIMIDINE SYSTEMS. XIX. A NEW SYNTHESIS OF PYRIDOU2,3-DOPYRIMIDINES. THE CONDENSATION OF 1,3-DIKETONES AND 3-KETOALDEHYDES WITH 4-AMINOPYRIMIDINES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,US,AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 80, no. 13, 5 July 1958 (1958-07-05), pages 3449-3457, XP002071946<br>ISSN: 0002-7863<br>table V, first entry<br>----   | 16                    |
| X          | WO 95 19774 A (WARNER LAMBERT CO)<br>27 July 1995 (1995-07-27)<br>claims 71,74<br>----   | 7,10,11,<br>15        |
| X          | WO 96 40142 A (PFIZER (US))<br>19 December 1996 (1996-12-19)<br>page 22, line 5 - line 16; claim 1<br>----   | 7,10,15               |
| P,X        | WO 98 46605 A (ABBOTT LAB)<br>22 October 1998 (1998-10-22)<br>the whole document<br>-----  | 1,7,10,<br>15,16      |

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